Review Article

Role of MMP inhibitors on levels of MMP-2 and MMP-9 in mammalian cell lines – A systematic review

Palak Jain[1], Alpa Gupta[1], Mrinalini[1], Mohit Sharma[2]

[1]Department of Conservative Dentistry and Endodontics, Manav Rachna Dental College, SDS, MRIIRS, Faridabad, Haryana, [2]Department of Oral Pathology, SGT Dental College Hospital and Research Institute, Gurugram, Haryana, India

Abstract

Matrix metalloproteinases (MMPs) are proteolytic enzymes involved in extracellular matrix (ECM) degradation, contributing to various pathological conditions, including periapical lesions and periodontal diseases. This systematic review evaluates the inhibitory effects of different natural and synthetic MMP inhibitors on MMP-2 and MMP-9 activities in mammalian cells, which are critical enzymes implicated in ECM breakdown. A comprehensive literature search was performed across databases, including PubMed, Scopus, and Cochrane until June 2023, following PRISMA guidelines. The Office of Health Assessment and Translation (OHAT) risk of bias tool was used for quality assessment, revealing a low risk of bias across all studies. Our findings demonstrate that both natural and synthetic MMP inhibitors significantly reduce MMP-2 and MMP-9 activities in mammalian cells. These compounds offer potential therapeutic benefits in managing diseases characterized by excessive MMP activity, such as periapical lesions and periodontal disease. This review highlights the therapeutic potential of MMP inhibitors in dentistry, specifically focusing on the promising roles of natural and synthetic MMP inhibitors in protecting ECM integrity.

Keywords: MMP-2, MMP-9, MMP inhibitors, mammalian cell lines

Address for correspondence: Dr. Alpa Gupta, Department of Conservative Dentistry and Endodontics, Manav Rachna Dental College, SDS, MRIIRS, Faridabad, Haryana, India.
E-mail: alpa.sds@mrei.ac.in

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INTRODUCTION

Collectively referred to as matrixins, MMPs constitute a multi-gene family within the metalloproteinase class of endopeptidases, wielding the potential to degrade a broad spectrum of ECM molecules, ranging from native to denatured collagen. Central to the breakdown of ECM are matrix metalloproteinases (MMPs), a diverse family of proteolytic enzymes ubiquitous in mammalian physiology, playing pivotal roles in both normal physiological processes and pathological events across various tissue types, including dental structures.[1]

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MMP-2 is present in cardiomyocytes, where it regulates mitochondrial function and stress signalling pathways, contributing to cellular homeostasis and response to physiological challenges. Meanwhile, MMP-9 is identified in neurons, where it plays a crucial role in modulating synaptic plasticity and neuroinflammatory responses, influencing neural communication and immune interactions in the brain.

Periradicular lesions, a consequence of bacterial infiltration into the dental pulp and root canal, represent

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a complex interplay of pathological events characterized by inflammation and the progressive destruction of alveolar bone and periapical tissues. This complicated process depends on the breakdown of the extracellular matrix (ECM), the structural backbone of connective tissue, orchestrating a cascade of molecular events that culminate in tissue breakdown and dysfunction.[2]

MMP activity is observed to exacerbate pulpal and periapical inflammation, thereby accelerating the rate of periapical bone lesion formation. MMP-9, in particular, may initiate bone resorption by ablating the collagen layer from the bone surface before the demineralization process.[3]

In the field of dentistry, exogenous inhibitors include a variety of synthetic and natural compounds that protect dentine and prevent demineralization by inhibiting the proteolytic activities of MMPs. Notable examples of these inhibitors are chlorhexidine, fluorinated products, indomethacin, tetracyclines, sodium trimetaphosphate, stannous chloride, benzalkonium chloride, ethanol and other alcohols, and quaternary ammonium compounds. Additionally, various crosslinking agents and medicinal plants, such as green tea, grape seed extracts, and curcumin, are renowned for their inhibiting impact on MMPs.[4,5]

MMP inhibitors hold significant therapeutic potential across various diseases. In cancer therapy, they help suppress tumour invasion and metastasis, enhancing chemotherapy efficacy and limiting metastatic spread. In inflammatory diseases such as arthritis and inflammatory bowel disease, they mitigate tissue damage by preventing MMP-mediated ECM degradation. Additionally, in cardiovascular conditions, these inhibitors play a crucial role in stabilizing plaques and slowing atherosclerosis progression, thereby reducing the risk of cardiovascular events.

MMP inhibitors (MMPIs) serve as adjunctive therapy in periodontitis treatment, complementing mechanical debridement and root planing by reducing excessive MMP activity to prevent tissue breakdown and bone resorption. Among pharmacological agents, doxycycline, particularly in sub-antimicrobial doses (SDD), is a well-studied MMPI that effectively limits periodontal tissue destruction while minimizing antibiotic resistance and systemic effects. Additionally, localized delivery systems such as gels, chips, and fibres have been developed to provide targeted MMP inhibition within periodontal pockets, enhancing treatment efficacy by reducing inflammation and promoting tissue regeneration.

Synthetic inhibitors include synthetic peptides, non-peptidic molecules, chemically modified tetracyclines, and bisphosphonates. These inhibitors have recently been going through clinical testing. Given the adverse effects of several synthetic MMPIs, interest has grown in natural substances that also inhibit MMPs. Natural products have long been a rich source of bioactive compounds, used either directly as drugs or as templates for synthetic modification. Various metabolites from several chemical categories, including anacardic acids, polysaccharides, and sulfated polysaccharides, directly inhibit MMPs or reduce their expression.[6]

Notable natural MMPIs include flavonoids and polyphenols. This diversity of structures provides a substantial framework for future research into natural product derivatives targeting MMP inhibition.[7]

In this systematic review, we focus on studies evaluating MMPIs tested on mammalian cells, specifically within the context of endodontic applications in dentistry. MMP-2 and MMP-9 play a critical role in the development of inflammatory periapical lesions, probably involved in the ECM degradation during the initial phase of lesion development. This focus is crucial as it represents a vital intermediary step before clinical application. Investigating the effects of MMPIs on mammalian cells provides essential insights into their efficacy, specificity, and potential side effects in a biological context that closely mimics human physiology. This approach bridges the gap between preliminary *in vitro* studies and real-world therapeutic applications, enhancing the reliability of future clinical interventions targeting MMP-related issues in endodontic treatments.[8]

MATERIALS AND METHODS

This systematic review was conducted in accordance to the transparent reporting guidelines of systematic reviews and meta-analysis (PRISMA) [Figure 1] with PICO format. Population (P) included the mammalian cells. Intervention (I) done was the use of an MMPI. Comparison (C) was with a control group without medication. Outcome (O) was measured in terms of the reduction of in MMP 2 and 9 levels. Two independent authors performed the data extraction after selecting the articles relevant to the review. Disagreements between the authors were resolved through meeting with a third reviewer. The third reviewer was consulted only for critical disagreement. The study has been registered in the open science framework, under DOI https://doi.org/10.17605/OSF.IO/NVYH6.

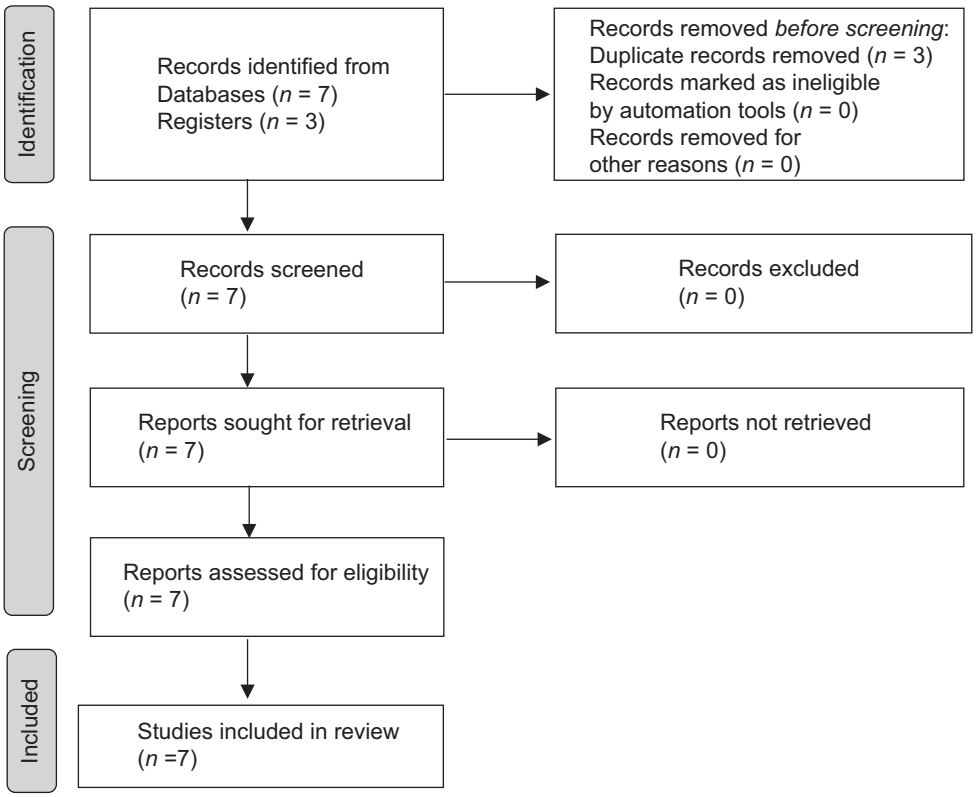

Figure 1: Prisma flow diagram 2020 depicting the flow from identification to screening and selecting the articles for systematic review

Search strategy

The laid-out literature search was conducted on electronic reference databases such as PubMed, Scopus, Cochrane, Web of Science, Cochrane Central Register of Controlled Trials (Central), and OpenGrey (www.opengrey.eu) until June 2023, and unpublished literature was searched on the clinical trial register (www.clinicaltrial.gov.in). The selected papers' list of references was additionally searched utilizing cross-referencing. MMP2 production, MMP-9, MMP-2, molecular docking studies, green tea catechins, and gingival fibroblasts are the mesh terms [Table 1]. These MeSH terms were combined using Boolean operators such as AND and OR to create a relevant search strategy that could be employed in the above-mentioned databases to identify articles that are applicable to the review question. As a result, these MeSH terms were chosen from the top of the mesh tree hierarchy to accommodate sub-headings.

Table 1: Search strategy applied to current review

Database	Search strategy
PubMed Scopus EBSCOhost	(("Inhibition of pro-/active MMP-2" AND "green tea catechins" AND "molecular docking studies") OR ("Effects of calcium hydroxide" AND "N-acetylcysteine" AND "MMP-2" AND "MMP-9" AND "TIMP-1" AND "TIMP-2" AND "LPS-stimulated macrophage cell lines") OR ("N-Acetylcysteine" AND "LPS-Induced Pro-inflammatory Cytokines" AND "MMP2 Production" AND "Gingival Fibroblasts") OR ("Inhibition of MMP-9" AND "green tea catechins" AND "molecular docking analysis") OR ("stannous chloride" AND "stannous fluoride" AND "inhibitors of matrix metalloproteinases") OR ("Grape Seed Extract" AND "Lipopolysaccharide-Induced Matrix Metalloproteinase Secretion" AND "Macrophages" AND ("MMP-1" OR "MMP-9")) OR ("Curcumin" AND "inhibits cell proliferation" AND "promotes apoptosis" AND "human osteoclastoma cell" AND "MMP-9" AND "NF-κB" AND "JNK signaling pathways"))

Selection criteria

Inclusion criteria

- Studies which include mammalian cell lines
- Studies which include MMP-2 and MMP-9
- Studies in English language
- Natural and synthetic MMP-2 and MMP-9 inhibitors.

Exclusion criteria

- Studies that do not use mammalian cell lines
- Studies that do not use MMP-2 and MMP-9
- Studies that use a language other than English.

Screening and selection

- The search strategy's findings were uploaded into the online screening tool Rayyan, which allowed the writers to screen the articles based on title and abstract. The selection criteria were studies that include mammalian cell lines, studies that use natural

Figure 2: Data extraction table

Author	Year	Journal	Type of study	Groups	Cells used	Outcome
Buzoglu, H. D., Aslanta[§], E.E., Aksoy, Y., Peynircioglu, B., Ceyhan, D.	2018	Turkish Journal of Biochemistry, 43 (6), pp. 571-7	*In vitro* study	• NAC group • Control group	• Human monocyte precursor cells (THP-1) differentiated into macrophage- adherent cells. • Unstimulated human macrophages.	• NAC decreases mRNA expression and protein levels of MMP-9. • Ca(OH)2 decreases mRNA expression of MMP-9 at 24 hours. • Both NAC and Ca(OH)2 decrease mRNA expression of MMP-2 at 24 hours, but NAC increases expression at 48 hours. NAC and Ca (OH) 2 decrease mRNA expression of TIMP-1 and TIMP-2 at 24 hours, but only NAC increases TIMP-1 expression at 48 hours.
Chowdhury, A., Nandy, S.K., Sarkar, J., Chakraborti, T., Chakraborti, S.	2017	Molecular and Cellular Biochemistry, 427 (1-2), pp. 111-22	*In vitro* study	• PASMCs culture with tea catechins • PASMCs culture without tea catechins	pulmonary artery smooth muscle cell (PASMC)	• EGCG and ECG inhibit pro-/active MMP-2 activities in PASMCs. • EGCG and ECG show strong interaction with MMP-2 and MT1- MMP. Better inhibition of proMMP-2 than MMP-2 by EGCG and ECG - EGCG and ECG inhibit MMP-9 activity in PASMC culture. - Molecular docking shows strong interaction between EGCG/ECG and MMP-9. - EGCG and ECG effectively prevent both proMMP-9 and MMP-9 activities. - EGCG and ECG may offer therapeutic benefits in preventing PAH.
Sarkar, J., Nandy, S.K., Chowdhury, A., Chakraborti, T., Chakraborti, S.	2016	Biomedicine and Pharmacotherapy, 84, pp. 340-7	*In vitro* study	• PASMC culture with tea extract • PASMC culture without tea extract	Pulmonary artery smooth muscle cells (PASMC s)	- LPS stimulates ROS production and pro-inflammatory cytokine expression in gingival fibroblasts. - NAC treatment suppresses LPS- induced inflammation by inhibiting ROS production, cytokine expression, and MMP-2 activity. - NAC blocks p38 MAPK and JNK activation, suggesting anti inflammatory effects. - Antioxidants like NAC could complement conventional periodontal treatments as adjunctive therapies.
Kim, D.Y., Jun, J.-H., Lee, H.-L., Baek, J.-H., Han, S.-B.	2007	Archives of Pharmacal Research, 30 (10), pp. 1283-92	*In vitro* study	Human gingival fibroblasts (GFs) treated with • Group A- lipopolysaccharide (LPS) from *E. coli,* • Group B- Actinobacillus actinomycetemco mitans, and • GROUP C - Porphyromonas gingivalis.	Human gingival fibroblasts (GFs)	
Fujiang Cao, Tao Liu, Yunqiang Xu, Dongdong Xu, Shiqing Feng	2015	International Journal of Clinical and Experimental Pathology	*In vitro* study	Group 1 - GCT cells treated with curcumin Group 2 - GCT cells with MMP-9 and curcumin	Human osteoclasto ma (Giant cell tumour, GCT) cells	Curcumin inhibits cell proliferation and promotes apoptosis in human osteoclastoma (Giant cell tumour, GCT) cells through suppression of MMP-9 and NF- kB, and activation of JNK signalling pathways. MMP-9 gene expression quantity was effectively reduced by treatment with curcumin

Contd...

Figure 2: Contd...

Author	Year	Journal	Type of study	Groups	Cells used	Outcome
Vu Dang La, Chantal Bergeron, Stefan Gafner, Daniel Grenier	2009	Journal of Periodontology	*In vitro* study	Group 1 - Macrophages stimulated with Aggregatibacter actinomycetemcomitans lipopolysaccharide (LPS) Group 2 - Macrophages 5.unstimulated with Aggregatibacter actinomycetemcomitans lipopolysaccharide (LPS)	Human monocyte- derived macrophag es.	Grape seed extract (GSE) inhibits the secretion of MMP-1, -3,-7,-8, -9, and-13 by LPS- stimulated macrophages and the activity of human recombinant MMP-1 and -9. This suppression is associated with the inhibition of NF-kB p65 and AP-1 activation.
Barbara Cvikl, Adrian Lussi, Thiago Saads Carvalho, Andreas Moritz, Reinhard Gruber	2019	Journal of Dentistry	*In vitro* study	Group 1 - (negative control) dentin samples that were neither etched nor treated Group 2 - samples that were treated with SnC 12, NaF, or SnF2	Human gingival fibroblasts and L929 mouse fibroblasts.	Stannous chloride (SnC 12) and stannous fluoride (SnF2) inhibit the proteolytic activity of MMP-2 and MMP-9. SnC 12 increases cell viability and proliferation, while CHX decreases cell viability. Sodium chloride (NaCl) had no inhibitory effect on MMPs. These findings suggest potential roles for SnC 12 and SnF2 in preventing dental erosion and caries.

and synthetic MMPIs, studies that evaluate the level of MMP-2 and MMP-9, and studies in the English language. The studies that did not use mammalian cell lines and which included MMP other than MMP-2 and MMP-9 and studies published in languages other than English were excluded from this review. To identify any papers that may have been missed during the preceding processes, reference lists of relevant articles and grey literature (OpenGrey) were searched. Figure 2 shows data extraction table of all the included studies

Quality assessment

Office of Health Assessment and Translation (OHAT) risk of bias assessment tool was applied to the current systematic review since OHAT is used when studies include both human and animal studies. In one of the study, gingival cells were obtained from patients with chronic periodontitis, whereas in other studies, laboratory-based fibroblast was used. The OHAT risk of bias assessment is a systematic approach used to evaluate the quality and potential biases in toxicological or environmental health studies. It focuses on specific domains such as selection bias, performance bias, detection bias, and reporting bias, amongst others. By applying structured criteria to these domains, the OHAT tool helps reviewers assess the reliability of study findings, ensuring a transparent and consistent evaluation of the research's internal validity. This method is particularly useful for informing regulatory decisions and health risk assessments. Figure 3 shows OHAT risk of assessment table.

OHAT risk of bias assessment tool revealed a definitely low risk of bias across all evaluated domains. Figure 4 reveals overall quality assessment of the included studies. This suggests that the study demonstrated strong methodological rigour, including clear participant selection, appropriate blinding, reliable outcome measurements, and complete reporting of data. This low risk of bias supports the study's validity and minimizes concerns of systematic error affecting the results.

DISCUSSION

This study investigated the inhibitory potential of natural and synthetic MMPIs on MMP-2 and MMP-9 activities in mammalian cells. Our analysis revealed that both natural and synthetic MMPIs significantly reduced the activities of these MMPs.

Matrix metalloproteinases (MMPs), including MMP-2 and MMP-9, play pivotal roles in inflammation and tissue remodelling, with their expression significantly elevated during pathological conditions such as periapical lesions.[9] Caley *et al.* observed a marked increase in MMP-2 and MMP-9 expression levels in non-healing compared to healing groups, highlighting their critical involvement in disease progression.[9] These results correspond with analysis conducted by Kruse *et al.*,[10] which reported higher MMP-2 and MMP-9 levels in symptomatic periapical lesions, suggesting their role in disease aetiology and progression.

Additionally, Torres *et al.*[11] demonstrated elevated MMP-2 expression in periapical granulomas, emphasizing MMPs' role in tissue remodelling under inflammatory conditions.

Figure 3: OHAT risk of assessment table

Study	Was administered dose or exposure level adequately randomized?	Was allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were The research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure character ization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Were there no other potential threats to internal validity (E.G., statistical methods were appropriate and researchers adhered to the study protocol)?
Buzoglu, H.D., Aslantaş, E.E., Aksoy, Y., .Peynircioglu, B., Ceyhan, D.	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias
Chowdhury, A., nandy, S.K., sarkar, J., chakraborti, T., chakraborti, S.	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias
sarkar, J., nandy, S.K., chowdhury, A., chakraborti, T., chakraborti, S.	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias
Kim, D.Y., jun, J.-H., lee, H.-L., .baek, J.-H., han, S.-B.	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias
Fujiang cao, tao liu, yunqiang xu, dongdong xu, shiqing feng	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias
Vu dang la, chantal bergeron, stefan gafner, daniel grenier	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias
Barbara cvikl, adrian lussi, thiago saads carvalho, andreas moritz, reinhard gruber	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely high risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias	Definitely low risk of bias

Figure 4: Quality assessment

Study	Definitely high risk of bias	Probably high risk of bias	Definitely low risk of bias	Probably low risk of bias
Buzoglu, H.D., Aslantaş, E.E., Aksoy, Y., Peynircioglu, B., Ceyhan, D.			Yes	
Chowdhury, A., Nandy, S.K., Sarkar, J., Chakraborti, T., Chakraborti, S.			Yes	
Sarkar, J., Nandy, S.K., Chowdhury, A., Chakraborti, T., Chakraborti, S.			Yes	
Kim, D.Y., Jun, J.-H., Lee, H.-L., Baek, J.-H., Han, S.-B.			Yes	
Fujiang Cao, Tao Liu, Yunqiang Xu, Dongdong Xu, Shiqing Feng			Yes	
Vu dang la, Chantal Bergeron, Stefan Gafner, Daniel Grenier			Yes	
Barbara Cvikl, Adrian Lussi, Thiago Saads Carvalho, Andreas Moritz, Reinhard Grube			Yes	

The study also noted increased MMP-9 expression due to DNA promoter region demethylation, indicating their role in ECM degradation within periapical lesions.[12,13]

Given the significant implications of MMPs in disease pathology, including their involvement in ECM degradation and tissue remodelling, therapeutic strategies have centred around suppressing their activity. Traditionally, exogenous MMPIs have focused on displacing the zinc-bound water molecule essential for MMP catalytic activity. On-going research have drifted in developing inhibitors with selective specificity, active site-directed potentials, and structural identification capabilities.[4]

In dentistry, synthetic and natural MMPIs offer diverse options for protecting dentin and preventing

demineralization. Noteworthy synthetic inhibitors include chemically modified tetracyclines (CMTs) like doxycycline, which inhibit MMP release and activity independently of their antimicrobial actions. Bisphosphonates, such as zoledronate, also inhibit MMP proteolytic activities and show promise in preventing dental caries progression.[14,15]

Natural compounds, such as green tea polyphenols (e.g., EGCG) and grape seed extract (GSE), demonstrate potent MMP inhibition. EGCG inhibits MMP-2 and MMP-9 directly and suppresses MMP activation by MT1-MMP, highlighting its potential in preserving dentin integrity.[7] GSE has shown efficacy in reducing MMP secretion and activity associated with periodontitis, indicating its purpose in preserving periodontal health.[16]

Despite promising preclinical findings, the clinical translation of MMPIs faces significant challenges. One major hurdle is bioavailability, as improving absorption and stability is essential to achieving therapeutic concentrations. Additionally, ensuring specificity is crucial to selectively targeting MMPs without disrupting normal ECM turnover required for tissue repair. Safety concerns also remain, as long-term use of MMPIs must minimize toxicity and adverse effects to ensure their viability as therapeutic agents.

Clinical studies underscore the efficacy of MMPIs in enhancing the integrity of hybrid layers in adhesive dentistry. Chlorhexidine digluconate (CHX), a widely used antimicrobial mouthwash, inhibits MMPs through a calcium-chelating mechanism, improving the longevity of dental restorations.[17]

Combined MMP therapies with conventional treatments will reduce MMP-mediated tissue destruction and enhance therapeutic outcomes in managing periodontal diseases.[18]

MMPIs can be integrated into current dental treatment protocols by serving as adjuncts to conventional therapies, enhancing clinical outcomes in periodontics, restorative dentistry, and endodontics. In periodontal therapy, sub-antimicrobial doses of doxycycline or locally delivered MMPIs (e.g., gels, chips) can be used alongside scaling and root planing to reduce tissue breakdown and promote regeneration. In restorative dentistry, incorporating MMPIs such as chlorhexidine or proanthocyanidins into dental adhesives can help stabilize collagen fibrils, improving bond strength and restoration longevity. In endodontics, MMPIs may aid in preserving pulp vitality and supporting periapical healing by mitigating ECM degradation. Their integration into treatment protocols could enhance long-term outcomes by minimizing tissue destruction and improving overall oral health.

Our results correspond with several previous studies. Catechins found in green tea have been reported to exhibit strong anti-MMP activities in various contexts. For example,[18] in his study reported the use of catechins found in green tea significantly limited MMP activity, aligning with our observations. Similarly, demonstrated that catechins effectively reduced MMP-2 and MMP-9 activities in cell culture models, supporting our results.[19]

The inhibition of MMP-2 and MMP-9 by catechins found in green tea and NAC has prominent implications for clinical applications. MMPs play a crucial role in ECM breakdown, contributing to various pathologies such as periapical lesions, periodontal disease, and cancer metastasis. By inhibiting these MMPs, green tea catechins and NAC could potentially mitigate ECM degradation, thereby providing a protective effect against tissue destruction.

One of the strengths of our study is the utilization of mammalian cell lines, which provide a appropriate model for human physiological processes and enable the study of MMP activity in a controlled environment.

The *in vivo* environment is substantially different, and inherent limitations of an *in vitro* replication may constrain our understanding of the systemic effects of MMPIs. Further studies on cultured cells and also *in vivo* studies of MMPIs are needed to define their toxicological profile before making them a part of the therapeutic regimen in periodontal treatment.

Researchers in the future should centre on validating our findings *in vivo* using animal models to study the effects of catechins found in green tea and NAC in a more complex biological context. Investigating the cellular processes that underpin their inhibitory effects could give further understanding into their potential therapeutic applications. Additionally, exploring the synergistic effects of combining green tea catechins and NAC with conventional treatments could enhance their efficacy.

Long-term studies are also needed to assess the sustained effect of these compounds on MMP activity and ECM integrity. Investigating the impact of different doses and treatment regimens could help optimize their therapeutic potential and minimize potential side effects.

CONCLUSION

In its entirety, our study demonstrates substantial proof for

the inhibiting capabilities of natural and synthetic MMPIs on MMP-2 and MMP-9 activities in mammalian cells. These findings highlight the potential of these compounds as therapeutic agents for preventing ECM degradation and managing conditions associated with elevated MMP activities. Further research is warranted to explore their clinical applications, optimize their therapeutic efficacy, and validate their long-term effects *in vivo*.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Brinckerhoff CE, Matrisian LM. Matrix metalloproteinases: A tail of a frog that became a prince. Nat Rev Mol Cell Biol 2002;3:207-14.
2. Tjäderhane L, Hotakainen T, Kinnunen S, Ahonen M, Salo T. The effect of chemical inhibition of matrix metalloproteinases on the size of experimentally induced apical periodontitis. Int Endod J 2007;40:282-9.
3. Manicone A, Mcguire J. Matrix metalloproteinases as modulators of inflammation. Semin Cell Dev Biol 2008;19:34-41.
4. Raeeszadeh-Sarmazdeh M, Do L, Hritz B. Metalloproteinases and their inhibitors: Potential for the development of new therapeutics. Cells 2020;9:1313.
5. Gobbi P, Maravic T, Comba A, Mazzitelli C, Mancuso E, Falconi M, *et al*. Biochemical and immunohistochemical analysis of tissue inhibitor of metalloproteinases-1 in human sound dentin. Clin Oral Invest 2021;25:5067-75.
6. Newman DJ, Cragg GM. Natural products as sources of new drugs from 1981 to 2014. J Nat Prod 2016;79:629-61.
7. Wang HMD, Chen CC, Huynh P, Chang JS. Exploring the potential of using algae in cosmetics. Bioresour Technol 2015;184:355-62.
8. Corotti MV, Zambuzzi WF, Paiva KB, Menezes R, Pinto LC, Lara VS, *et al*. Immunolocalization of matrix metalloproteinases-2 and-9 during apical periodontitis development. Arch Oral Biol 2009;54:764-71.
9. Caley MP, Martins VLC, O'Toole EA. Metalloproteinases and wound healing. Adv Wound Care (New Rochelle) 2015;4:225-34.
10. Kruse C, Spin-Neto R, Christiansen R, Wenzel A, Kirkevang LL. Periapical bone healing after apicectomy with and without retrograde root filling with mineral trioxide aggregate: A 6-year follow-up of a randomized controlled trial. J Endod 2016;42:533-7.
11. Torres AFC, Antunes LS, de Oliveira NF, Küchler EC, Gomes CC, Antunes LAA. Genetic polymorphism and expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in periapical lesions: Systematic review. J Endod 2020;46:3-11.e1.
12. Dezerega A, Madrid S, Mundi V, Valenzuela MA, Garrido M, Paredes R, *et al*. Pro-oxidant status and matrix metalloproteinases in apical lesions and gingival crevicular fluid as potential biomarkers for asymptomatic apical periodontitis and endodontic treatment response. J Inflamm (Lond) 2012;9:8.
13. Martinho FC, Teixeira FFC, Cardoso FGR, Ferreira NS, Nascimento GG, Carvalho CAT, *et al*. Clinical investigation of matrix metalloproteinases, tissue inhibitors of matrix metalloproteinases, and matrix metalloproteinase/tissue inhibitors of matrix metalloproteinase complexes and their networks in apical periodontitis. J Endod 2016;42:1082-8.
14. Gialeli C, Theocharis AD, Karamanos NK. Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. FEBS J 2011;278:16-27.
15. Mukherjee PK, Maity N, Nema NK, Sarkar BK. Natural matrix metalloproteinase inhibitors. In: Studies in Natural Products Chemistry. Elsevier; 2013. p. 91-113.
16. Villas Boas SB, Sousa LS, Cardoso LM, Tavella-Silva NC, de Souza Costa CA, Basso FG. Grape seed extract down-modulates oxidative and inflammatory responses of oral mucosa cells. J Int Acad Periodontol 2021;23:301-7.
17. Boelen GJ, Boute L, d'Hoop J, EzEldeen M, Lambrichts I, Opdenakker G. Matrix metalloproteinases and inhibitors in dentistry. Clin Oral Invest 2019;23:2823-35.
18. Aslantaş EE, Aksoy Y, Akkaya Ulum YZ, Ceyhan D, Peynircioglu B, Buzoğlu HD. Effects of calcium hydroxide and N-acetylcysteine on MMP-2, MMP-9, TIMP-1 and TIMP-2 in LPS-stimulated macrophage cell lines. Turk J of Biochemistry 2018;43:571-7.
19. Chowdhury A, Nandy SK, Sarkar J, Chakraborti T, Chakraborti S. Inhibition of pro-/active MMP-2 by green tea catechins and prediction of their interaction by molecular docking studies. Mol Cell Biochem 2017;427:111-22.