Assessment of Acetic Acid Interaction with MMP-8 and MMP-9: Implications for Dentin Matrix Degradation in Early Childhood Caries - An in silico study

Sneha Harshini[1], Dr. Ramesh R[2], Dr. Mahesh R[3], Dr. Prijitha Alex[4], Dr. Aiswarya Ann Babu[5], Dr. Riny George[6*]

[1] Resident Dental Intern, Department of Pediatric Dentistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai – 600077, Tamil Nadu, India.
(snehaharshini@gmail.com)

[2] PhD Scholar, Assistant Professor, Department of Pediatric Dentistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, 160, Poonamallee High Road, Vellappanchavadi, Chennai – 600077, Tamil Nadu, India.
(162415013.sdc@saveetha.com)

[3] PhD Guide, Professor & Head of Academics, Department of Pediatric Dentistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, 160, Poonamallee High Road, Vellappanchavadi, Chennai – 600077, Tamil Nadu, India.
(mahesh@saveetha.com)

[4] Professor & Head, Department of Public Health Dentistry, Al-Azhar Dental College, Thodupuzha, Kerala, India.
(priji01@gmail.com)

[5] Reader, Department of Pediatric and Preventive Dentistry, Al-Azhar Dental College, Thodupuzha, Kerala, India.

[6] Senior Lecturer, Department of Oral and Maxillofacial Surgery, Al-Azhar Dental College, Thodupuzha, Kerala, India.
(rinygt@gmail.com)
ORCID: 0009-0004-0767-0928

Corresponding Author:

Dr. Ramesh R[2]*
Assistant Professor, Department of Pediatric Dentistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai – 600077, Tamil Nadu, India.
Email: 162415013.sdc@saveetha.com

Abstract: Background: Early childhood caries (ECC) is a multifactorial disease characterized by progressive demineralization and degradation of dental hard tissues. Acetic acid, a metabolic by-product of cariogenic bacteria, contributes to the acidic environment associated with caries progression. Matrix metalloproteinases (MMPs), particularly MMP-8 and MMP-9, play crucial roles in dentin collagen degradation following demineralization.
Aim: To evaluate the molecular interaction of acetic acid with MMP-8 and MMP-9 using an in silico molecular docking approach and assess its potential implications in dentin matrix degradation associated with ECC.
Materials and Methods: Three-dimensional structures of MMP-8 (PDB ID: 1BZS) and MMP-9 (PDB ID: 1GKC) were retrieved from the Protein Data Bank. Acetic acid (PubChem CID: 176) was used as the ligand. Molecular docking was performed using PyRx integrated with AutoDock Vina, and protein–ligand interactions were analyzed using BIOVIA Discovery Studio Visualizer.
Results: Acetic acid demonstrated weak binding affinities toward MMP-8 and MMP-9, with docking scores of −3.2 kcal/mol and −3.1 kcal/mol, respectively. MMP-8 exhibited hydrogen bonding, aromatic interactions, and zinc-associated contacts, whereas MMP-9 interactions were predominantly mediated through van der Waals forces.
Conclusion: Acetic acid showed limited direct interaction with MMP-8 and MMP-9. Its contribution to ECC may be primarily indirect through maintenance of an acidic microenvironment that promotes dentin demineralization and facilitates MMP-mediated collagen degradation..
Keywords: Early Childhood Caries; Matrix Metalloproteinase 8; Matrix Metalloproteinase 9; Dentin; Molecular Docking Simulation, Good Health and Well-Being; Clean Water and Sanitation; Pediatric Dentistry

Introduction

Early childhood caries (ECC) remains one of the most prevalent chronic diseases affecting children worldwide and continues to pose a significant public health burden despite advances in preventive dentistry.[1] The disease is characterized by the progressive destruction of dental hard tissues resulting from the interaction between cariogenic microorganisms, fermentable carbohydrates, host factors, and environmental influences. While the role of bacterial biofilms in initiating enamel demineralization is well established, increasing evidence suggests that host-derived mechanisms contribute substantially to the progression of dentinal caries lesions.[2],[3],[4]

The metabolism of dietary carbohydrates by cariogenic bacteria, particularly Streptococcus mutans and Lactobacillus species, results in the production of organic acids, including lactic acid, acetic acid, formic acid, and propionic acid. Among these, acetic acid is a significant metabolic by-product present within cariogenic biofilms and contributes to the sustained acidic environment responsible for tooth demineralization. The prolonged reduction in pH not only promotes mineral loss from enamel and dentin but also facilitates the activation of endogenous proteolytic enzymes embedded within the dentin matrix.[5],[6]

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases involved in extracellular matrix remodeling and collagen degradation. Among them, MMP-8 and MMP-9 have been extensively implicated in the progression of dentinal caries. MMP-8, also known as neutrophil collagenase, degrades type I collagen, the major organic component of dentin, whereas MMP-9 contributes to the degradation of denatured collagen and gelatin fragments generated during the carious process.[7],[8] Following acid-mediated demineralization, the exposed collagen matrix becomes susceptible to enzymatic degradation by activated MMPs, thereby accelerating dentin destruction and lesion progression.

Previous investigations have primarily focused on the activation of MMPs under acidic conditions and their elevated expression in carious dentin. Studies have demonstrated increased levels of MMP-8 and MMP-9 in active carious lesions, highlighting their role in dentin matrix breakdown and disease progression.[9],[10] However, the molecular mechanisms through which specific bacterial metabolites interact with these enzymes remain poorly understood. Although acetic acid is recognized as an important organic acid produced during bacterial fermentation, its direct interaction with MMP-

8 and MMP-9 has received limited attention in the dental literature.

A notable gap exists in understanding whether acetic acid can directly bind to or influence the structural and functional behavior of dentin-associated matrix metalloproteinases. Most available studies have investigated the effects of acidic environments on MMP activation but have not explored the molecular interaction between individual organic acids and these enzymes. Elucidating such interactions may provide valuable mechanistic insights into the pathways linking bacterial metabolism to dentin matrix degradation in ECC.

In silico molecular docking offers a rapid and cost-effective approach for evaluating ligand–protein interactions and predicting binding affinity at the molecular level. Therefore, the present study aims to assess the interaction of acetic acid with MMP-8 and MMP-9 using computational docking techniques. Understanding these interactions may contribute to a better understanding of the molecular events involved in dentin degradation and provide a foundation for future investigations into host–microbial interactions in early childhood caries.

MATERIALS AND METHODS

Study Design

This study was designed as an in silico molecular docking investigation to evaluate the interaction of acetic acid with matrix metalloproteinases implicated in dentin matrix degradation during early childhood caries. Molecular docking was performed using PyRx 0.8 integrated with the AutoDock Vina docking engine, a widely used computational platform for predicting ligand–protein interactions and binding affinities.[9],[11]

Protein Selection and Preparation

Matrix metalloproteinase-8 (MMP-8) and matrix metalloproteinase-9 (MMP-9) were selected as target proteins because of their established roles in collagen degradation and dentin matrix breakdown during caries progression.[9],[10],[7] The three-dimensional crystal structures of MMP-8 (PDB ID: 1BZS) and MMP-9 (PDB ID: 1GKC) were retrieved from the Protein Data Bank (PDB), an internationally recognized repository for experimentally determined macromolecular structures.[12]

Protein preparation was carried out using BIOVIA Discovery Studio Visualizer (Dassault Systèmes BIOVIA, San Diego, CA, USA). Prior to docking, all water molecules, co-crystallized ligands, and non-essential heteroatoms were removed to prevent interference with ligand binding predictions. Missing hydrogen atoms were added, and the prepared protein structures were saved in Protein Data Bank (PDB) format for subsequent docking analysis.[13]

Ligand Retrieval and Preparation

Acetic acid was selected as the ligand for the present study because it is a major organic acid produced during bacterial fermentation within cariogenic dental biofilms and contributes to the acidic microenvironment associated with dentin demineralization.[1] The three-dimensional conformer of acetic acid (PubChem CID: 176) was obtained from the PubChem database in Structure Data File (SDF) format.[14]

The ligand structure was imported into PyRx and subjected to energy minimization using the Open Babel module to obtain a stable conformation before docking. The minimized ligand was then converted into the PDBQT format required for AutoDock Vina calculations.[15]

Molecular Docking Procedure

Molecular docking simulations were performed using PyRx version 0.8 employing the AutoDock Vina algorithm, which predicts the most energetically favorable binding orientation between a ligand and its target protein. The prepared protein and ligand structures were imported into the PyRx workspace. For each protein, a docking grid box was generated around the catalytic domain to ensure adequate coverage of the potential ligand-binding region. Docking parameters were maintained at the default AutoDock Vina settings with an exhaustiveness value of 8. Multiple docking poses were generated for each protein–ligand complex, and the pose exhibiting the lowest binding energy (kcal/mol) was selected as the most favorable interaction conformation.[15],[16],[16]

Analysis of Protein–Ligand Interactions

The best-ranked docking conformations were exported and analyzed using BIOVIA Discovery Studio Visualizer. Two-dimensional and three-dimensional interaction maps were generated to identify hydrogen bonds, van der Waals interactions, electrostatic interactions, and hydrophobic contacts between acetic acid and amino acid residues present within the binding pockets of MMP-8 and MMP-9. The interacting amino acid residues, number of hydrogen bonds, and nature of intermolecular interactions were documented and compared between the two proteins to determine potential differences in binding behavior.[17]

Evaluation of Binding Affinity

Binding affinity was assessed using AutoDock Vina docking scores expressed in kilocalories per mole (kcal/mol). More negative binding energy values were considered indicative of stronger ligand–protein interactions and greater theoretical binding stability. In addition to docking scores, interaction profiles and residue-level contacts were evaluated to support interpretation of the binding mechanism.

Visualization of Docked Complexes

Graphical representations of docked complexes were generated using Discovery Studio Visualizer. Protein ribbon structures, ligand-binding conformations, and two-dimensional interaction diagrams were prepared to illustrate the molecular interactions between acetic acid and the target proteins. These visualizations facilitated qualitative assessment of the binding mode and interaction pattern within the catalytic region of MMP-8 and MMP-9.[18]

Statistical Analysis

As the study was entirely computational and generated deterministic docking scores rather than biological measurements, inferential statistical analysis was not performed. Binding affinities and molecular interaction profiles were analyzed descriptively and compared qualitatively between MMP-8 and MMP-9.

RESULTS

Figure 1A

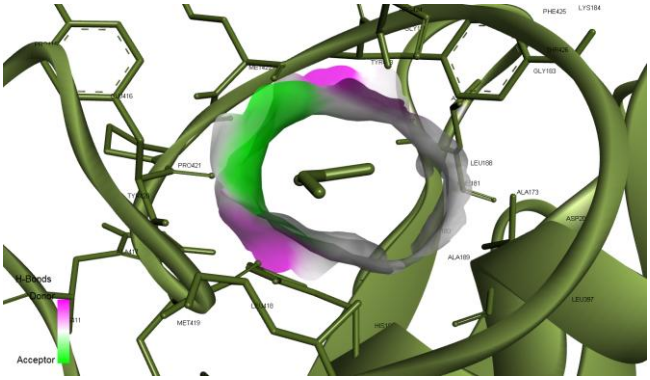

Figure 1B

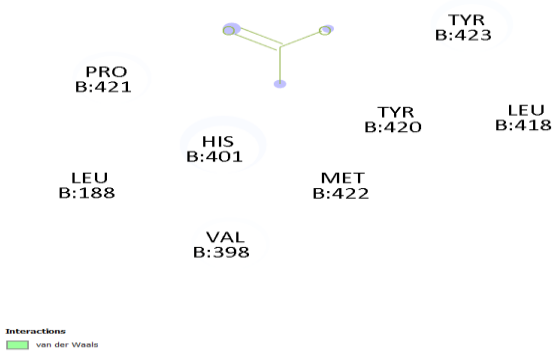

Figure 1C

Figure 1: Molecular docking analysis of acetic acid with MMP-9 (PDB ID: 1GKC). (A) Surface representation of the ligand within the MMP-9 binding cavity. (B) Three-dimensional visualization of the docked acetic acid–MMP-9 complex showing the ligand orientation within the active-site region. (C) Two-dimensional interaction map illustrating residue-level contacts with Val398, His401, Leu188, Pro421, Tyr420, Met422, Tyr423, and Leu418. The best-ranked docking pose exhibited a binding affinity of −3.1 kcal/mol and was stabilized predominantly by van der Waals interactions.

The acetic acid molecule occupied a hydrophobic pocket of MMP-9 and was stabilized mainly through weak van der Waals interactions with surrounding amino acid residues. Although acetic acid demonstrated weak direct binding to MMP-9, its role in ECC may primarily be indirect through

acidification of the dentin microenvironment, which promotes demineralization and facilitates activation of endogenous matrix metalloproteinases. Acetic acid demonstrated a maximum binding affinity of −3.1 kcal/mol toward MMP-9. The best-ranked docking pose was localized within a surface-accessible binding cavity and was stabilized predominantly through van der Waals interactions. Residues involved in ligand recognition included His401, Val398, Leu188, Pro421, Tyr420, Met422, Tyr423, and Leu418. No hydrogen bonding interactions were observed between acetic acid and MMP-9. The relatively low binding affinity suggests a weak interaction between the ligand and the enzyme. These findings indicate that acetic acid may not directly modulate MMP-9 activity through strong binding interactions; however, its contribution to an acidic microenvironment may indirectly facilitate dentin matrix degradation during early childhood caries.

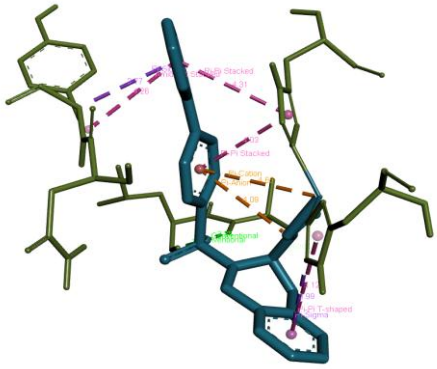

Figure 2: Three-dimensional molecular docking analysis of acetic acid with MMP-8 (PDB ID: 1BZS). The ligand is positioned within the catalytic binding pocket of MMP-8 and exhibits interactions with surrounding amino acid residues. Multiple non-covalent interactions, including hydrogen bonding, pi-cation interactions, and aromatic stacking interactions, contribute to ligand stabilization within the active-site region.

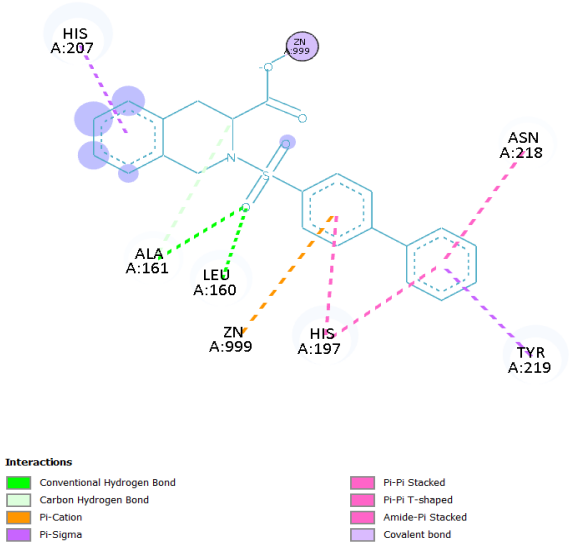

Figure 3: Two-dimensional interaction map of the acetic acid–MMP-8 complex. Acetic acid interacted with Ala161, Leu160, His197, His207, Asn218, and Tyr219 through conventional hydrogen bonds, carbon hydrogen bonds, pi-cation interactions, pi-sigma interactions, and pi-pi stacking interactions. Interaction with the catalytic zinc ion (Zn^{2+}) was also observed.

Acetic acid demonstrated a maximum binding affinity of −3.2 kcal/mol toward MMP-8 (PDB ID: 1BZS). The ligand occupied the catalytic pocket and interacted with several amino acid residues including Ala161, Leu160, His197, His207, Asn218, and Tyr219. The docking analysis revealed the presence of conventional hydrogen bonds, carbon hydrogen bonds, pi-cation interactions, pi-sigma interactions, and pi-pi stacking interactions. The ligand exhibited interactions with the catalytic zinc ion (Zn^{2+}), an essential cofactor involved in the enzymatic activity of MMP-8. The observed binding pattern suggests that acetic acid can establish weak yet diverse molecular contacts within the active-site region of MMP-8. However, the relatively low binding affinity indicates limited direct binding stability. These findings suggest that acetic acid may contribute to dentin matrix degradation primarily through environmental acidification rather than through strong direct modulation of MMP-8 activity.

Protein	**PDB ID**	**Best Binding Affinity (kcal/mol)**	**Major Interacting Residues**	**Major Interaction Types**
MMP-8	1BZS	-3.2	Ala161, Leu160, His197, His207, Asn218, Tyr219, Zn^{2+}	Conventional hydrogen bond, Carbon hydrogen bond, Pi-cation, Pi-sigma, Pi-pi stacking, Zn interaction
MMP-9	1GKC	-3.1	Val398, His401, Leu188, Pro421, Tyr420, Met422, Tyr423, Leu418	Predominantly van der Waals interactions

Table 1: Molecular Docking Scores of Acetic Acid Against MMP-8 (1BZS) and MMP-9 (1GKC)

Acetic acid exhibited weak binding affinities toward both MMP-8 and MMP-9, with the strongest interaction observed for MMP-8 (−3.2 kcal/mol). MMP-8 demonstrated a more diverse interaction profile involving hydrogen bonding, aromatic interactions, and catalytic zinc coordination, whereas MMP-9 interactions were primarily stabilized by van der Waals contacts.

Acetic acid exhibited weak binding affinity toward both matrix metalloproteinases investigated. The highest binding affinity was observed with MMP-8 (−3.2 kcal/mol), followed by MMP-9 (−3.1 kcal/mol). MMP-8 displayed a greater number of stabilizing interactions, including hydrogen bonds, pi-cation interactions, and zinc-associated contacts, whereas MMP-9 showed predominantly van der Waals interactions. These findings suggest limited direct interaction of acetic acid with dentin-associated MMPs, supporting the hypothesis that its role in ECC progression is more likely mediated through environmental acidification and subsequent activation of endogenous matrix metalloproteinases.

DISCUSSION

The present in silico study evaluated the interaction of acetic acid, a major organic acid produced by cariogenic microorganisms, with MMP-8 and MMP-9, two matrix metalloproteinases implicated in dentin matrix degradation during early childhood caries (ECC). The docking analysis demonstrated weak binding affinities for acetic acid against both MMP-8 (−3.2 kcal/mol) and MMP-9 (−3.1 kcal/mol). Although the binding energies were relatively low, distinct interaction patterns were observed. MMP-8 exhibited conventional hydrogen bonding, carbon hydrogen bonding, pi-cation interactions, pi-sigma

interactions, aromatic stacking interactions, and catalytic zinc-associated interactions, whereas MMP-9 showed predominantly van der Waals interactions. These findings suggest that acetic acid may establish direct molecular contact with dentin-associated MMPs; however, the interaction strength appears insufficient to support a strong inhibitory or modulatory role.

The role of bacterial metabolic products in ECC has gained increasing attention in recent years. Heimisdottir et al.[19] demonstrated that children with ECC exhibit distinct plaque metabolomic profiles characterized by altered biochemical metabolites associated with disease progression. Their findings support the concept that metabolic products generated by cariogenic biofilms contribute significantly to the pathological environment responsible for dental hard tissue destruction. The present study extends this concept by investigating one such metabolite, acetic acid, at the molecular level and evaluating its interaction with enzymes involved in dentin degradation.

Similarly, Kim et al. [20] identified organic acid-related salivary metabolites as potential biomarkers of ECC and reported significant alterations in metabolite signatures among affected children. These observations reinforce the biological relevance of bacterial metabolic products in ECC. Although our docking results demonstrated weak direct binding between acetic acid and MMPs, they support the broader hypothesis that microbial metabolites may participate in disease progression through mechanisms extending beyond demineralization alone.

Li et al. [21] reported that severe ECC is associated with profound alterations in salivary microbiome and metabolome composition. The authors suggested that microbial metabolic activity plays a central role in disease progression. The weak docking affinities observed in the present study indicate that acetic acid may not act as a potent direct regulator of MMP activity. Instead, its contribution may be indirect through maintenance of an acidic microenvironment that favors activation of endogenous matrix metalloproteinases and collagen degradation.

Further supporting this concept, Pan et al. [22] demonstrated significant metabolomic differences in saliva from children with ECC and emphasized the importance of microbial metabolites in disease pathogenesis. Acetic acid is a common end product of bacterial fermentation and contributes to pH reduction within dental biofilms. Acidic conditions are known to expose collagen fibrils by demineralizing dentin, thereby facilitating MMP-mediated degradation. Consequently, the role of acetic acid in ECC may be more closely related to environmental modification than direct enzyme regulation.

Proteomic studies have also highlighted the importance of host-derived factors in ECC. Huang et al.[23] identified numerous salivary proteins associated with ECC development and progression, suggesting that host responses play a critical role in disease susceptibility. Similarly, Oliveira et al. [24] demonstrated significant alterations in salivary protein expression profiles among children with ECC. These findings align with the current understanding that host-derived proteases, including MMP-8 and MMP-9, contribute substantially to dentin matrix degradation following acid-mediated demineralization.

A comprehensive review by Zhang et al.[25] emphasized the growing importance of omics technologies in understanding the complex biological networks involved in caries progression. Their review highlighted metabolomics and proteomics as promising approaches for identifying interactions between microbial products and host pathways. The present study complements these observations by providing a preliminary computational assessment of a microbial metabolite–host enzyme interaction.

Direct comparison with molecular docking studies involving MMPs is also informative. Salman et al.[26] investigated cinnamic acid derivatives as potential MMP inhibitors and reported substantially

stronger binding affinities than those observed in the present study. Their findings suggest that structurally complex phytochemicals may effectively modulate MMP activity through stable interactions with catalytic residues. In contrast, acetic acid demonstrated only weak binding, likely due to its small molecular size and limited functional groups available for interaction.

Guo et al.[27] demonstrated strong inhibitory interactions between theaflavins and MMP-2 using molecular docking and molecular dynamics simulations. Compared with theaflavins, acetic acid lacks the structural complexity required for extensive hydrogen bonding and hydrophobic interactions. This may explain the relatively weak binding energies observed against MMP-8 and MMP-9 in the present study.

The observations of Elgezawi et al. [28] are particularly relevant to the interpretation of our findings. Their review emphasized that matrix metalloproteinases are central mediators of dentin collagen degradation and contribute significantly to caries progression. The current results support the importance of MMP-8 and MMP-9 in ECC while suggesting that acetic acid itself may not directly regulate their activity. Instead, acetic acid likely contributes indirectly by promoting acidic conditions that facilitate enzyme activation and substrate exposure.

These findings indicate that acetic acid exhibits only weak direct molecular interactions with MMP-8 and MMP-9 and its biological significance in ECC should not be underestimated, as its primary role may involve environmental acidification, demineralization of dentin, and facilitation of host-derived proteolytic processes. These findings contribute to the growing understanding of host–microbial interactions involved in ECC progression.

The strength of this study is that it provides preliminary insight into the interaction of acetic acid with MMP-8 and MMP-9, two key enzymes involved in dentin matrix degradation during early childhood caries, thereby enhancing understanding of host–microbial interactions in caries progression. However, the findings are limited by the use of molecular docking alone without molecular dynamics simulations or experimental validation, and the small molecular size of acetic acid may restrict interaction complexity. Future studies should incorporate molecular dynamics, enzyme activity assays, and cell-based experiments, while also evaluating other cariogenic organic acids such as lactic, propionic, and formic acids to better elucidate their role in dentin matrix degradation and ECC pathogenesis.

CONCLUSION

Within the limitations of this computational study, acetic acid demonstrated only modest affinity toward MMP-8 and MMP-9, indicating that direct ligand–enzyme interactions are unlikely to be the primary mechanism underlying its contribution to early childhood caries. The stronger interaction profile observed with MMP-8 compared to MMP-9 suggests potential differences in protein recognition; however, both interactions remained weak overall. These findings support the concept that acetic acid may exert its pathogenic influence predominantly through environmental acidification, thereby creating conditions favorable for dentin demineralization and subsequent matrix metalloproteinase activation. This study provides a novel molecular perspective on the relationship between bacterial metabolites and dentin degradation and establishes a foundation for future investigations exploring the role of organic acids in ECC pathogenesis.

References

Tinanoff N, Baez RJ, Guillory D. Early childhood caries epidemiology, risk assessment, and prevention. Pediatr Dent. 2019;41(6):425–31.

Janani, Ramesh R, Ramakrishnan M. Association of salivary catalase activity and oxidative stress in early childhood caries: A biomarker for caries risk. Journal of South Asian Association of Pediatric Dentistry [Internet]. 2026 Mar 5;9(1):51–6. Available from: http://dx.doi.org/10.5005/jp-journals-10077-3403

Chaussain C, Boukpessi T, Khaddam M, Tjaderhane L, George A, Menashi S. Dentin matrix degradation by host matrix metalloproteinases: inhibition and clinical perspectives toward regeneration. Front Physiol [Internet]. 2013 Nov 1;4:308. Available from: http://dx.doi.org/10.3389/fphys.2013.00308

Kishorwara R, Devika PS, Madhumitha M, Mohanprasanth A, Snega R. Structural and optical characteristics of green-synthesized ZnO/SrO nanocomposites using pomegranate peel extract and their biological activity. Next Mater [Internet]. 2026 Jul;12(102006):102006. Available from: http://dx.doi.org/10.1016/j.nxmate.2026.102006

Joshy R, Ramesh D, Mahesh D. Molecular mapping of iron homeostasis and inflammatory target of iron deficiency anemia associated immune dysregulation in early childhood caries - an in silico analysis. Int J Drug Deliv Technol [Internet]. 2026 Apr 23;16(16s). Available from: http://dx.doi.org/10.25258/ijddt.16.16s.85

Assessment of Antimicrobial Efficacy of Saffron -Withania Somnifera Herbal gel Against oral ulcers-An Invitro Study.

Takahashi N, Nyvad B. The role of bacteria in the caries process: ecological perspectives. J Dent Res [Internet]. 2011 Mar;90(3):294–303. Available from: http://dx.doi.org/10.1177/0022034510379602

Mahalingam M, Pillai DS, Muthupandian S. Assessment of anti-inflammatory and antioxidant properties of trypsin, bromelain, rutoside and glucosamine combination gel: An in-vitro study. J Clin Diagn Res [Internet]. 2026 Jan 1; Available from: http://dx.doi.org/10.7860/jcdr/2025/79703.22219

Tjäderhane L, Buzalaf MAR, Carrilho M, Chaussain C. Matrix metalloproteinases and other matrix proteinases in relation to cariology: the era of "dentin degradomics." Caries Res [Internet]. 2015 Feb 6;49(3):193–208. Available from: http://dx.doi.org/10.1159/000363582

Joshy R, Ramesh D, Mahesh D. Structural insights into curcumin interaction with inflammatory cytokines and proliferative protein targets in early childhood caries - an in silico docking study. Int J Drug Deliv Technol [Internet]. 2026 Apr 9;16(6s). Available from: http://dx.doi.org/10.25258/ijddt.16.6s.91

Sulkala M, Tervahartiala T, Sorsa T, Larmas M, Salo T, Tjäderhane L. Matrix metalloproteinase-8 and -9 in dentin and carious lesions. Caries Res. 2007;41(4):296–303.

Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods Mol Biol [Internet]. 2015;1263:243–50. Available from: http://dx.doi.org/10.1007/978-1-4939-2269-7_19

Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem [Internet]. 2010 Jan 30;31(2):455–61. Available from: http://dx.doi.org/10.1002/jcc.21334

Kim S, Chen J, Cheng T. PubChem in 2023: new data content and improved web interfaces. Nucleic Acids Res. 2023;51(D1):D1373–80.

Berman HM, Westbrook J, Feng Z. The Protein Data Bank. Nucleic Acids Res. 2000;28(1):235–42.

Senthil R, Angamuthu D, Geetha Sravanthy P, Pradeep Kumar R. Integrative nanoformulation of paclitaxel, ruthenium (II), and curcumin for enhanced oral cancer cell suppression. J Oral Biol Craniofac Res [Internet]. 2025 Nov;15(6):1824–30. Available from: http://dx.doi.org/10.1016/j.jobcr.2025.10.024

Sruthi MA, Mani G, Ramakrishnan M, Selvaraj J. Dental caries as a source of Helicobacter pylori infection in children: An RT-PCR study. Int J Paediatr Dent [Internet]. 2023 Jan;33(1):82–8. Available from: http://dx.doi.org/10.1111/ipd.13017

BIOVIA Discovery Studio Visualizer v24.1.0.23298. Dassault Systèmes. San Diego, CA, USA;

Heimisdottir LH, Lin BM, Cho H, Orlenko A, Ribeiro AA, Simon-Soro A, et al. Metabolomics insights in early childhood caries. J Dent Res [Internet]. 2021 Jun;100(6):615–22. Available from: http://dx.doi.org/10.1177/0022034520982963

Kim S, Song Y, Kim S, Kim S, Na H, Lee S, et al. Identification of a biomarker panel for diagnosis of early childhood caries using salivary metabolic profile. Metabolites [Internet]. 2023 Feb 27;13(3):356. Available from: http://dx.doi.org/10.3390/metabo13030356

Li K, Wang J, Du N, Sun Y, Sun Q, Yin W, et al. Salivary microbiome and metabolome analysis of severe early childhood caries. BMC Oral Health [Internet]. 2023 Jan 19;23(1):30. Available from:

http://dx.doi.org/10.1186/s12903-023-02722-8

Pan T, Ren Y, Li J, Liao Y, Xing X. Polymicrobial detection and salivary metabolomics of children with early childhood caries. PeerJ [Internet]. 2025 May 6;13:e19399. Available from: http://dx.doi.org/10.7717/peerj.19399

Huang S, Tian W, Tian J, Tang H, Qin M, Zhao B, et al. Deep saliva proteomics elucidating the pathogenesis of early childhood caries and identifying biomarkers for early prediction. J Proteome Res [Internet]. 2025 Feb 7;24(2):750–61. Available from: http://dx.doi.org/10.1021/acs.jproteome.4c00831

Oliveira BP, Buzalaf MAR, Silva NC, Ventura TMO, Toniolo J, Rodrigues JA. Saliva proteomic profile of early childhood caries and caries-free children. Acta Odontol Scand [Internet]. 2023 Apr;81(3):216–26. Available from: http://dx.doi.org/10.1080/00016357.2022.2118165

Zhang JS, Huang S, Chen Z, Chu CH, Takahashi N, Yu OY. Application of omics technologies in cariology research: A critical review with bibliometric analysis. J Dent [Internet]. 2024 Feb;141(104801):104801. Available from: http://dx.doi.org/10.1016/j.jdent.2023.104801

Salman M, Asgartooran B, Taherkhani A. Targeting matrix metalloproteinase-3 for dental caries prevention using herbal isolates: MMP3 inhibition by cinnamic acids. Int J Dent [Internet]. 2024 Oct 8;2024:9970824. Available from: http://dx.doi.org/10.1155/2024/9970824

Guo J, Hu M, Yang M, Cao H, Li H, Zhu J, et al. Inhibition mechanism of theaflavins on matrix metalloproteinase-2: inhibition kinetics, multispectral analysis, molecular docking and molecular dynamics simulation. Food Funct [Internet]. 2024 Jul 15;15(14):7452–67. Available from: http://dx.doi.org/10.1039/d4fo01620c

Elgezawi M, Haridy R, Almas K, Abdalla MA, Omar O, Abuohashish H, et al. Matrix metalloproteinases in dental and periodontal tissues and their current inhibitors: Developmental, degradational and pathological aspects. Int J Mol Sci [Internet]. 2022 Aug 11;23(16):8929. Available from: http://dx.doi.org/10.3390/ijms23168929.

.