Evaluation of Syzygium Cumini as MMP Inhibitor in Human Dentin: an In-Vitro Study

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**Abstract:** The bond strength at the dentin-adhesive interface diminishes over time due to hydrolytic degradation of dentin collagen, which weakens the interface stability. Inhibiting collagen-degrading enzymes, such as matrix metalloproteinases (MMPs), particularly MMP-9 can enhance bond durability by protecting collagen fibers within the adhesive layer, thus prolonging the lifespan of the restoration. *Syzygium cumini* extract has anti-inflammatory properties but its role as MMP-9 inhibitor is yet to be explored. This study potentially explores the inhibitory effect on MMP-9 and for enhancing the longevity of composite restoration.To determine the inhibitory effect of *Syzygium cumini* on MMP-9 in dentin collagenEthanolic extracts of *Syzygium cumini* were prepared and applied to demineralized human dentin samples. Two different concentrations of the extract (100 µg and 200 µg) were tested. MMP-9 activity levels were measured and analyzed by ELISA to determine the inhibition efficacy of the extract.The results were dose-dependent inhibiting MMP-9 activity, with a remarkable decrease in MMP-9 activity at 200 µg concentration as compared with 100 µg of the *S. cumini* extract. This further postulates that higher doses of *S. cumini* significantly inhibit MMP-9 activity in human dentin.*S. cumini* can potentially improve the stability of dentin-resin interfaces. Future clinical trials are recommended to validate its application in dentistry and broader health contexts.

Keywords: Collagen degradation, matrix metalloproteinases, *Syzygium cumini*,

# Introduction

*Syzygium cumini*, popularly known as jamun, is one of the tropical, evergreen fruit-bearing tree species native to the Indian subcontinent.[(Qamar et al., 2022)](https://paperpile.com/c/1qXiuo/mB4yx) This species has been used for decades in medicine based on its several pharmacological activities; it exhibits anti-inflammatory activity, radical-scavenging activity, and antimicrobial activity.[(Qamar et al., 2021)](https://paperpile.com/c/1qXiuo/GQmdP) The matrix metalloproteinases represent a family of the zinc-dependent endopeptidases, which relate to great importance in the degradation process of the components of the extracellular matrix. [(Tjäderhane, 2015)](https://paperpile.com/c/1qXiuo/qHqsJ) Among these, MMP-9 plays an important role in many physiological and pathological processes such as tissue remodeling, wound healing, and inflammation.[(Sorsa et al., 2004)](https://paperpile.com/c/1qXiuo/eakZl) It had been implicated in the pathogenesis of periodontal disease and dental caries in relation to dental health, wherein the over expression resulted in the breakdown of dentinal collagen.[(Jain & Bahuguna, 2015)](https://paperpile.com/c/1qXiuo/AftJ1) Regulation of the activity of MMP-9 is hence of essence since it contributes to the prevention of destruction of tissues and maintaining oral health.[(Ajay et al., 2023; Chokkattu et al., 2023; Padarthi et al., 2023)](https://paperpile.com/c/1qXiuo/NXl37+wWl6d+FoSp3)ls of *Syzygium cumini* in modulating the activity of MMP. Phytochemical constituents extracted from the fruit and other parts of the plant, including flavonoids, tannins, and phenolic acids, possess strong anti-inflammatory and antioxidant activities[(Keerthana & Ramesh, 2021; Murugesan, 2021; Subramanian et al., 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/1qXiuo/4wE16+5osmn+tseyv+AVcd1). For example, compounds such as ellagic acid and quercetin have been identified in *Syzygium cumini* that may prove responsible for MMP activities, thus they probably prevent the degradation of tissues. [(Ahmed et al., 2019; Kumari et al., 2023)](https://paperpile.com/c/1qXiuo/dsDHl+f4g5R) Such phytochemicals may downregulate the expression of MMP-9, thereby contributing to the integrity of dentin[(Keerthana & Ramesh, 2021; Murugesan, 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/1qXiuo/4wE16+5osmn+tseyv).The compound possesses the property of MMP inhibition as well as in vitro antagonism against some of the pathogenic oral bacteria such as Streptococcus mutans and Porphyromonas gingivalis [(Ramakrishnan et al., 2023; Shenoy & Maiti, 2023; J. S. Sindhu et al., 2023)](https://paperpile.com/c/1qXiuo/4VlNb+G3GgI+Gy1IQ). Since *Syzygium cumini* possesses both MMP inhibitory activity and antimicrobial activity, it could be used as a promising dental therapeutic candidate [(Kasabwala et al., 2021; Rajeshkumar & Lakshmi, 2021; Varghese et al., 2023)](https://paperpile.com/c/1qXiuo/M61Kp+zTCu4+8g5Z4).The extract acts through adjustment of pro-inflammatory cytokine expression [(Pranati et al., 2021; Sakthi 2021)](https://paperpile.com/c/1qXiuo/BRPOm+XBCLU). In recent times, much attention has been paid to the therapeutic potential. These are known to upregulate the expression of MMP-9. Alternatively, an antioxidant property may decrease the content of oxidative stress, a factor known to enhance the activity of MMP. In-vitro study on assessing the efficacy of *Syzygium cumini* extracts as inhibitors of MMP-9 of human dentin[(Dharman et al., 2023; S. Sindhu et al., 2023; Sreenivasagan et al., 2023)](https://paperpile.com/c/1qXiuo/qLuij+2ZqhT+NaQ6y). This study will address the interaction of *Syzygium cumini* with MMP-9 and hence provide useful information regarding the possible application of this natural product in the prevention and management of dental diseases due to activation of MMP.

# Materials and methods

## Preparation of *Syzygium cumini* Extract

The dried leaves of *Syzygium cumini* extract was prepared under the following conditions and steps for quality and sterility: Healthy leaves were chosen and washed with running tap water followed by sterilization through immersion in a 70% ethanol solution for 5-10 minutes, and rinsed with sterile distilled water. The leaves, post-sterilization, were dried in a drying oven at 40-50°C to prevent the degradation of the bioactive compounds. After drying, the leaves were milled into fine powder for storage in well-closed containers until extraction. Extraction: Soxhlet extraction was carried out with ethanol to utilize all the available bioactive compounds by making maximum recovery. After extraction, ethanol was removed using a rotary evaporator under reduced pressure, while leaving concentrated residue; the latter was then further concentrated, and kept at -20°C for later use. The meticulous care taken in the above procedure had made sure that the final extract was of good quality and free from contamination by microbes. (Figure 1)



**Figure-1:** Preparation of ethanolic plant extract at different concentrations: Ethanolic plant extracts of Syzygium cumini were prepared at various concentrations. Group 1 was given a positive control with the standard MMP inhibitor, doxycycline. Group 2 received 100 µg of the extract. Group 3 received 200 µg. Group 4 received no treatment and thus was a negative control.

# Sample Collection and Preparation of Human Dentin

15 healthy extracted premolars that were extracted for orthodontic purposes were collected, after obtaining informed consent from the patients and clearance from the institutional review board. The selection criteria included healthy teeth that were free from dental caries. The extracted teeth were decontaminated by removing all organic matter and pulp tissue, then powdered into very fine dentin powder using a pestle and mortar under cryogenic conditions (-80°C) to prevent heat degradation of the dentin matrix.

## Demineralization of Dentin

Demineralize the dentin powder by incubation with 10% phosphoric acid (v/v) at room temperature for 30 minutes. The acid was then removed gently and the dentin is neutralized by washing it in 1 M NaOH until its pH becomes that of neutrality or pH 7.0. The dentin powder was then washed 3 times using deionized water, and it is left air-dry to be used further in the experiment.

## Experimental Design

The experiments were divided into four groups:

- Group 1: The sample was treated with a positive control and applied with a standard MMP inhibitor using doxycycline.

- Group 2: Treated with 100 µg Syzygium cumini extract

- Group 3: Treated with 200 µg of Syzygium cumini extract

- Group 4: Negative control without treatment.

Each group was provided with the same mass of dentin powder that was incubated with their respective treatments. The samples of all the groups were incubated in phosphate buffered saline (PBS) at 37°C for 24 hours.

# Measurement of MMP Activity

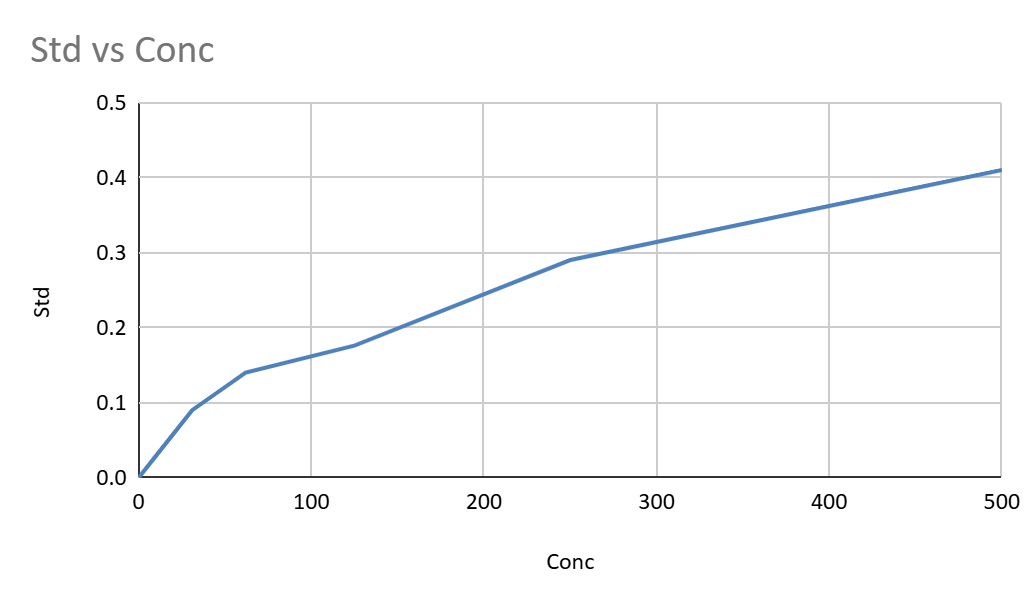
After incubation, the dentin powders were collected and activity of matrix metalloproteinase (MMP-9) was measured by using the specific ELISA kits bought for MMP-9. ELISA kits were used according to the company's guidelines.Samples were added to ELISA plates, and the absorbance was read at 450 nm using a microplate reader. The results were processed to find the concentration of MMP-9 for each group.

# Statistical Analysis

Data are expressed as mean ± standard deviation (SD). Differences among the groups were compared statistically by using one-way analysis of variance (ANOVA) for the differences to be significant across the groups. A difference at a p-value < 0.05 was considered statistically significant.

# Results

A standard curve for ELISA analysis, was established which allows for the determination of MMP-9 concentrations in unknown samples based on their OD values.(Graph 1)

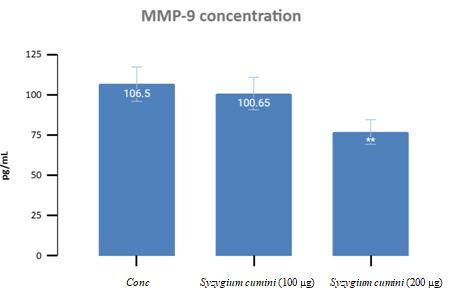
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**Figure 2:** Each point on the graph corresponds to an OD value for a known concentration of MMP-9. As the concentration of MMP-9 increases, the OD value also increases, indicating a direct relationship.

The ELISA analysis demonstrated a clear dose-dependent inhibitory effect of Syzygium cumini on MMP-9 concentration. As the dose increased from 100 µg to 200 µg, the mean MMP-9 levels progressively decreased, indicating enhanced inhibition at higher concentrations. (Table 1) This trend suggests that Syzygium cumini effectively suppresses MMP-9 expression, highlighting its potential role in regulating matrix metalloproteinase activity as displayed in Graph 2. The reduction in MMP-9 levels with increasing doses supports the hypothesis that Syzygium cumini exerts its inhibitory effects in a concentration-dependent manner.Furthermore, the precision of measurements was confirmed by relatively low standard error of the mean (SEM) values across all experimental groups.(Table 2) These low SEM values indicate high reliability and consistency in the data, reducing the likelihood of variability affecting the observed results. This strengthens the validity of the findings and reinforces the conclusion that Syzygium cumini has a measurable and reproducible impact on MMP-9 inhibition.

**Table 1:** The table presents OD values and corresponding MMP-9 concentrations (pg/mL) for three different treatment groups: control, *Syzygium cumini* (100 µg), and *Syzygium cumini* (200 µg).

| **Sample.No** | **Group name** | **OD Value** | **pg/ml** |
| --- | --- | --- | --- |
| 1 | Control | 0.159 | 112.9 |
| 1 | Control | 0.141 | 100.1 |
| 2 | *Syzygium cumini (100µg)* | 0.14 | 99.4 |
| 2 | *Syzygium cumini (100µg)* | 0.143 | 101.6 |
| 3 | *Syzygium cumini (200µg)* | 0.09 | 63.9 |
| 3 | *Syzygium cumini (200µg)* | 0.101 | 71.7 |



**Figure 3:** The graph provides data on the mean concentration of MMP-9 (in pg/mL) and the standard error of the mean (SEM) for different treatment groups.

**Table 2:** The table provides data on the mean concentration of MMP-9 (in pg/mL) and the standard error of the mean (SEM) for different treatment groups.

|  | **Concentration** | ***Syzygium cumini(100µg)*** | ***Syzygium cumini(200µg)*** |
| --- | --- | --- | --- |
| Mean | 106.5 | 100.65 | 76.8 |
| SEM | 6 | 7 | 5 |

# Discussion

The study presents evidence of the significant dose-dependent inhibitory effects of Syzygium cumini on Matrix Metalloproteinase-9 (MMP-9) concentrations in human dentin. Notably, higher concentrations of Syzygium cumini (200 µg) demonstrated more pronounced inhibition compared to lower concentrations (100 µg). These findings suggest that Syzygium cumini may serve as a natural inhibitor of MMPs, potentially playing a crucial role in preserving the integrity of the dentin matrix and inhibiting tissue degradation. The results align with previous research highlighting the anti-inflammatory and antioxidant properties of Syzygium cumini, reinforcing its relevance in addressing collagen degradation by MMP. Chlorhexidine is the most studied MMP inhibitor and has demonstrated most efficient effectiveness in preserving the collagen structure within the hybrid layer, but its long-term stability remains a concern due to its large, water-soluble nature Over time, chlorhexidine may leach out of the hybrid layer, leading to a reduction in its protective effects.[(Breschia et al., 2010)](https://paperpile.com/c/1qXiuo/WjPZ)Studies have shown that while collagen activity can be preserved for up to six months, the hybrid layer's integrity begins to degrade after one year.[(Francisconi-dos-Rios et al., 2015)](https://paperpile.com/c/1qXiuo/KNojv) Additionally, studies have indicated that chlorhexidine exhibits cytotoxic effects on odontoblast-like cells and stem cells derived from human exfoliated deciduous teeth, emphasizing the need for careful consideration of chlorhexidine's use in dentistry.[(Tu et al., 2015)](https://paperpile.com/c/1qXiuo/IyAKR) This highlights the need for the development of more stable, long-lasting inhibitors or alternative approaches that provide sustained protection against enzymatic degradation, ensuring longer-lasting dental restorations.In recent years, the use of plant extracts and traditional treatments have gained widespread popularity. Research has shown that Grape seed extract, green tea extract, cranberry extract have been utilized as natural inhibitors of matrix metalloproteinases (MMPs), targeting enzymatic activity responsible for collagen degradation and contributing to the preservation of tissue integrity in dental applications.[(Wang et al., 2021)](https://paperpile.com/c/1qXiuo/55fMf) Syzygium cumini has demonstrated a dose-dependent inhibitory effect on MMP-9, similar to other natural inhibitors such as turmeric, green tea, and grape seed extract.[(Carvalho et al., 2016; Hermansyah et al., 2024; Kumar et al., 2019)](https://paperpile.com/c/1qXiuo/nifGt+G23uP+UnK10) Curcumin, the active compound in turmeric, has been widely studied for its anti-inflammatory and MMP-inhibitory properties, particularly against MMP-9(Saadh et al., 2024). Similarly, green tea polyphenols, especially epigallocatechin gallate (EGCG), have shown strong inhibitory effects on MMP-9 expression, reducing extracellular matrix degradation(Almatrafi et al., 2024). Vitis vinifera contains proanthocyanidins, which have been found to suppress MMP-9 activity and protect connective tissue integrity.[(Puzari et al., 2022)](https://paperpile.com/c/1qXiuo/9gb4E) While all these natural compounds exhibit MMP-9 inhibition, Syzygium cumini stands out due to its distinct flavonoid and tannin composition, which may provide a unique mechanism of action.

The findings of the present study show significant results and they suggest that Syzygium cumini extract could be a promising natural alternative to synthetic MMP inhibitors, which are often used to preserve dentin during dental restorative procedures. By inhibiting MMP-9, the extract may help maintain the structural integrity of dentin and prevent degradation, potentially improving the longevity of dental restorations

# Conclusion

The findings of this study demonstrate that Syzygium cumini acts as an effective inhibitor of human dentinal matrix metalloproteinase-9 (MMP-9) in a dose-dependent manner. The significant reduction in MMP-9 levels with increasing concentrations highlights its potential therapeutic application in conditions associated with excessive MMP-9 activity. Further research is warranted to explore its mechanisms of action and potential clinical benefits.

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