Evaluation of Pisum Sativum as MMP Inhibitor in Human Dentin:an In Vitro Study

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**ABSTRACT:** Matrix metalloproteinases (MMPs) are critical in the degradation of dentin extracellular matrix, posing a challenge to the durability of dental restorations. This in vitro study explores the inhibitory effects of *Pisum sativum* (pea) extract on MMP activity in human dentin, with the goal of enhancing the longevity of resin-dentin bonds. The study findings suggest that *Pisum sativum* extract significantly inhibits MMP activity, preserving dentin structure and potentially extending the lifespan of restorative materials. These results indicate the potential for *Pisum sativum* extract to be developed into a natural therapeutic agent in dental applications.The aim of this study was to determine the degree to which ethanolic *Pisum sativum* might inhibit the MMP-9 concentration within human dentin as a possible therapeutic treatment to promote better dental hygiene.Ethanolic extracts of *Pisum sativum* 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 to determine the inhibition efficacy of the extract.The results were dose-dependently inhibiting MMP-9 activity, with a remarkable decrease in MMP-9 activity at 200 µg concentration as compared with 100 µg of the *Pisum sativum* extract. This further postulates that higher doses of *Pisum sativum* may significantly inhibit MMP-9 activity in human dentin.A standard curve is used to determine MMP-9 concentrations in unknown samples. In the control group, MMP-9 concentration is 106.5 pg/mL. With 100 µg of *Pisum sativum* extract, it decreases to 72 pg/mL (32.4% inhibition), and with 200 µg, it drops to 46.15 pg/mL (56.7% inhibition).The data shows that *Pisum sativum* extract inhibits MMP-9 activity in a dose-dependent manner. Higher extract concentrations lead to greater inhibition, suggesting its potential to reduce MMP-9-mediated dentin degradation, which could be beneficial in dental treatments.

**KEYWORDS:** *Pisum sativum,* MMP inhibitors, dentin matrix, in vitro study, dental biomaterials, resin-dentin bond longevity, natural therapeutics

# INTRODUCTION

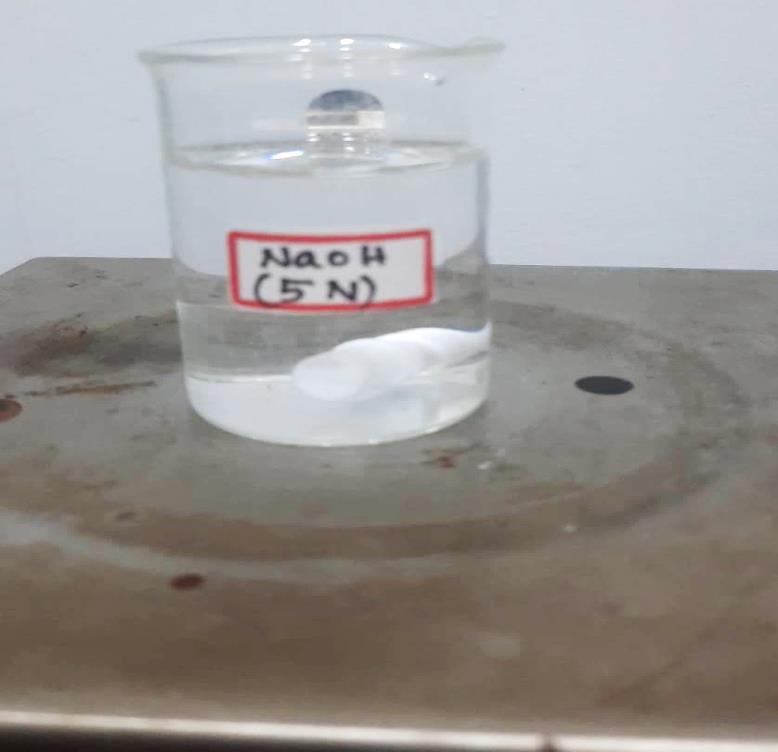
Matrix metalloproteinases (MMPs) are zinc-dependent enzymes responsible for the degradation and remodelling of extracellular matrix structures, such as collagen and elastin. In dentistry, MMPs are known to contribute to the deterioration of the dentin organic matrix following demineralization, which can reduce the effectiveness and longevity of resin-dentin bonds used in restorations. The use of acidic etching agents in adhesive procedures activates MMPs in the dentin, accelerating collagen breakdown and ultimately leading to the failure of these bonds over time.[(Cabral-Pacheco et al., 2020)](https://paperpile.com/c/WJ2rWA/adfx)The pursuit of effective MMP inhibitors has been a key area of dental research, aiming to protect the dentin matrix and extend the durability of dental restorations [(Ajay et al., 2023; Chokkattu et al., 2023; Padarthi et al., 2023)](https://paperpile.com/c/WJ2rWA/fnptJ+p5lV2+T7BoV). Synthetic MMP inhibitors like chlorhexidine have proven to be effective, but their prolonged use has raised concerns about possible cytotoxic effects and the risk of developing antimicrobial resistance [(Dharman et al., 2023; S. Sindhu et al., 2023; Sreenivasagan et al., 2023)](https://paperpile.com/c/WJ2rWA/xDyv0+docEv+V9HvQ). As a result, there is increasing interest in discovering natural inhibitors that are not only effective but also biocompatible.[(Zheng & Chen, 2017)](https://paperpile.com/c/WJ2rWA/u0bR)This shift toward natural alternatives highlights a growing recognition of the limitations associated with synthetic compounds in clinical applications[(Pranati et al., 2021; Sakthi & 2021)](https://paperpile.com/c/WJ2rWA/iExQR+YCyJy). Chlorhexidine, while widely used for its antimicrobial and MMP-inhibiting properties, can cause damage to surrounding oral tissues when used over extended periods [(Keerthana & Ramesh, 2021; Murugesan, 2021; Subramanian et al., 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/WJ2rWA/GZ2Gn+3AxLa+uVbHy+BEPCE). Additionally, the rise of antimicrobial resistance presents a significant challenge, as it diminishes the long-term efficacy of such treatments, potentially leading to more complex oral health issues [(Keerthana & Ramesh, 2021; Murugesan, 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/WJ2rWA/GZ2Gn+3AxLa+uVbHy)[(Brookes et al., 2020)](https://paperpile.com/c/WJ2rWA/9pgk).In contrast, natural MMP inhibitors, derived from plant extracts or other biocompatible sources, offer a promising solution [(Ramakrishnan et al., 2023; Shenoy & Maiti, 2023; J. S. Sindhu et al., 2023)](https://paperpile.com/c/WJ2rWA/BxXE+UxgE+KyVf). They are often less toxic to human tissues and less likely to contribute to antimicrobial resistance[(Al AlSheikh et al., 2020)](https://paperpile.com/c/WJ2rWA/fhGH). These natural compounds may provide a safer option for regular use in dental care, particularly in procedures involving resin-dentin bonds or other restorative treatments that require long-term integrity[(Zhang et al., 2017)](https://paperpile.com/c/WJ2rWA/Sf8f). Researchers are actively exploring natural substances for their ability to inhibit MMPs effectively while supporting overall oral health, (Saadh et al., 2024) presenting a sustainable and safer alternative to synthetic inhibitors [(Kasabwala et al., 2021; Rajeshkumar & Lakshmi, 2021; Varghese et al., 2023)](https://paperpile.com/c/WJ2rWA/X8Ws1+zc87h+pb1Ug). This exploration could lead to the development of novel therapeutic strategies that improve dental treatment outcomes and (Almatrafi et al., 2024) reduce the risks associated with long-term synthetic drug use.[(de Moraes et al., 2020)](https://paperpile.com/c/WJ2rWA/BDoz)Pisum sativum, commonly known as the pea plant, is a legume abundant in bioactive compounds such as flavonoids, tannins, and polyphenols. These compounds have been recognized for their diverse biological activities, including anti-inflammatory, antioxidant, and anti-proteolytic effects[(Wu et al., 2023)](https://paperpile.com/c/WJ2rWA/TzBN). Such properties make Pisum sativum an attractive candidate for research as a natural inhibitor of matrix metalloproteinases (MMPs), particularly in the context of dental health. MMPs play a significant role in the breakdown of dentin, a key component in the durability of dental restorations.[(Elgezawi et al., 2022)](https://paperpile.com/c/WJ2rWA/ySZ4)Given these characteristics, the current study focuses on assessing the potential of Pisum sativum extract to inhibit MMP activity in human dentin. By using an in vitro experimental approach, the research aims to determine whether the bioactive compounds in the pea plant can effectively reduce MMP-driven collagen degradation in dentin. If successful, Pisum sativum extract could offer a natural, biocompatible alternative to synthetic MMP inhibitors, helping to prolong the lifespan of dental restorations and protect oral tissues from degradation[(Rungruangmaitree & Jiraungkoorskul, 2017)](https://paperpile.com/c/WJ2rWA/I5Un). This investigation not only highlights the therapeutic potential of natural plant-based solutions in dentistry but also aligns with the growing interest in sustainable, non-toxic treatments in oral health care.[(Website, n.d.-a)](https://paperpile.com/c/WJ2rWA/4psa)

# MATERIALS AND METHODS

## Preparation of *Pisum sativum* Extract

Dried leaves of *Pisum sativum* were obtained, washed, and air-dried in a controlled environment to prevent contamination. The dried leaves were then finely ground into a powder. Ethanol (70%) was used as the solvent for extraction, with the leaf powder subjected to maceration for 48 hours at room temperature with constant stirring. The ethanol extract was filtered, concentrated using a rotary evaporator under reduced pressure, and stored at -20°C. Before use in experiments, the extract was reconstituted in dimethyl sulfoxide (DMSO) to prepare working solutions of desired concentrations.

## Preparation of Human Dentin Powder



1. (b)
2. **Figure- 1:** Preparation of Demineralized Dentin Powder: Acid Treatment and Neutralization Process

Human premolars, extracted for orthodontic purposes, were collected following informed consent and ethical approval. The teeth were cleaned and sectioned to isolate the dentin, which was then ground into a fine powder using a cryogenic mill to ensure consistency and minimise thermal degradation. The dentin powder was demineralized by treating it with 10% phosphoric acid for 24 hours, which removes the mineral content and exposes the organic matrix. After demineralization, the dentin powder was neutralised by washing with 1 M sodium hydroxide (NaOH) until a neutral pH was achieved. The neutralised dentin powder was rinsed with phosphate-buffered saline (PBS) and stored at 4°C until further use.

## Experimental Groups

The study included four groups to assess the effect of Pisum sativum extract on MMP-9 activity:

Group 1: Control (PBS-treated): Dentin powder incubated in PBS without any treatment, serving as the baseline for MMP-9 activity.

Group 2: Negative Control (DMSO-treated): Dentin powder treated with DMSO alone to account for any effects of the solvent used in reconstituting the Pisum sativum extract.

Group 3: Positive Control (Doxycycline-treated): Dentin powder treated with doxycycline, a known synthetic MMP inhibitor, to provide a benchmark for comparison.

Group 4: Test Groups (100 μg and 200 μg *Pisum sativum* extract): Dentin powder treated with two different concentrations of *Pisum sativum* extract (100 μg and 200 μg) to evaluate the dose-dependent effect of the extract on MMP-9 activity.

## Incubation and Treatment Protocol

Each group of dentin powder was incubated in PBS at 37°C for 24 hours with their respective treatments (PBS, DMSO, doxycycline, or *Pisum sativum* extract). The incubation period allowed the treatments to interact with the dentin matrix and potentially inhibit MMP-9 activity.

## Measurement of MMP-9 Activity

After incubation, the MMP-9 activity in each sample was quantified using an enzyme-linked immunosorbent assay (ELISA) kit specific for human MMP-9. The ELISA kit measures the concentration of active MMP-9 by detecting the enzyme’s ability to cleave a specific substrate linked to a colorimetric reporter. The absorbance of the reaction product was measured at 450 nm using a microplate reader. The absorbance values were directly proportional to the MMP-9 activity in the samples.

# Statistical Analysis

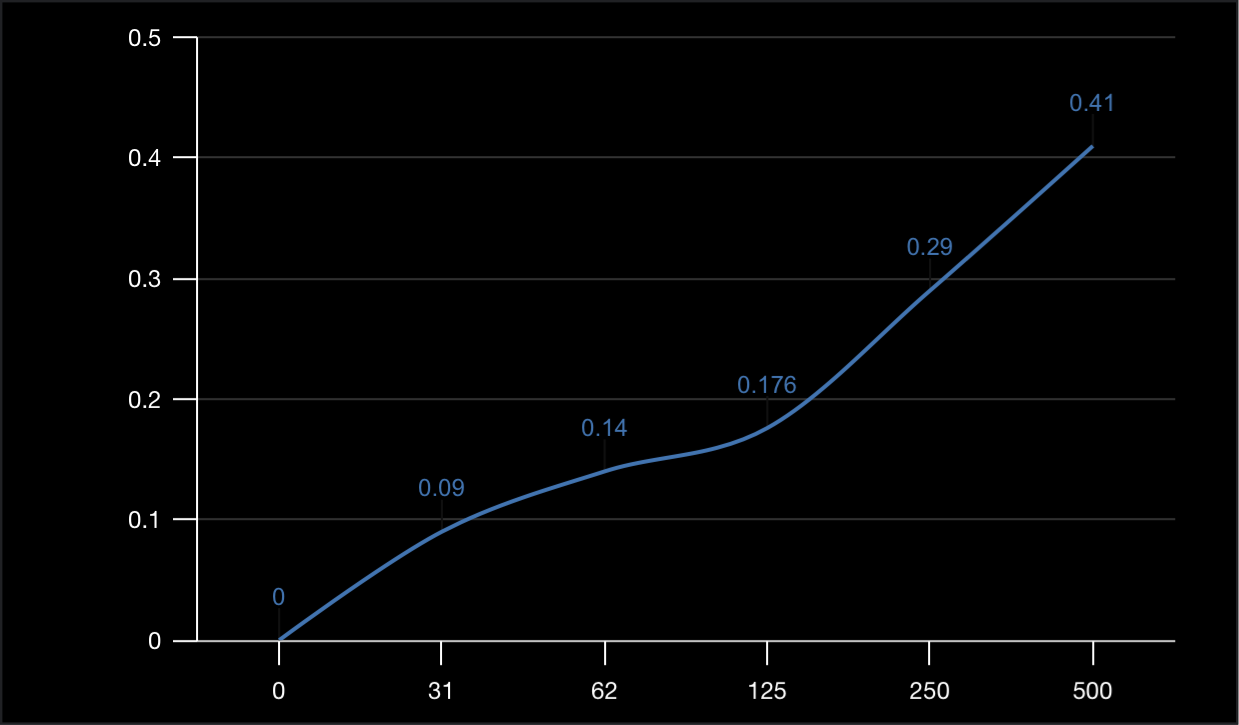
The data were analysed and presented as mean ± standard deviation (SD). Statistical comparisons between the groups were made using one-way analysis of variance (ANOVA) followed by post hoc testing to determine significant differences among groups. A p-value < 0.05 was considered statistically significant, indicating that the observed differences were not due to random chance. SPSS software (version 25.0) was used for all statistical analyses.

# Results

**Table-1:** The table provided lists the known concentrations of MMP-9 and their corresponding Optical Density (OD) values. This data is typically used to create a standard curve for ELISA analysis, which allows for the determination of MMP-9 concentrations in unknown samples based on their OD values.

|  |  |
| --- | --- |
| Conc | Std |
| 0 | 0 |
| 31 | 0.09 |
| 62 | 0.14 |
| 125 | 0.176 |
| 250 | 0.29 |
| 500 | 0.41 |

## MMP-9 standard



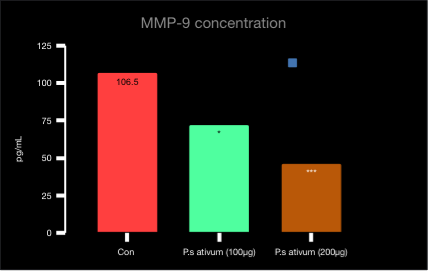
**Figure-4:** Each point on the graph corresponds to an OD value for a known concentration of MMP-9. As the concentration of MMP-9 increases, the OD value also increases, indicating a direct relationship.

**Table-2:** The table presents OD values and corresponding MMP-9 concentrations (pg/mL) for three different treatment groups: control, *pisum sativum* (100 µg), and (200 µg) *pisum sativum*

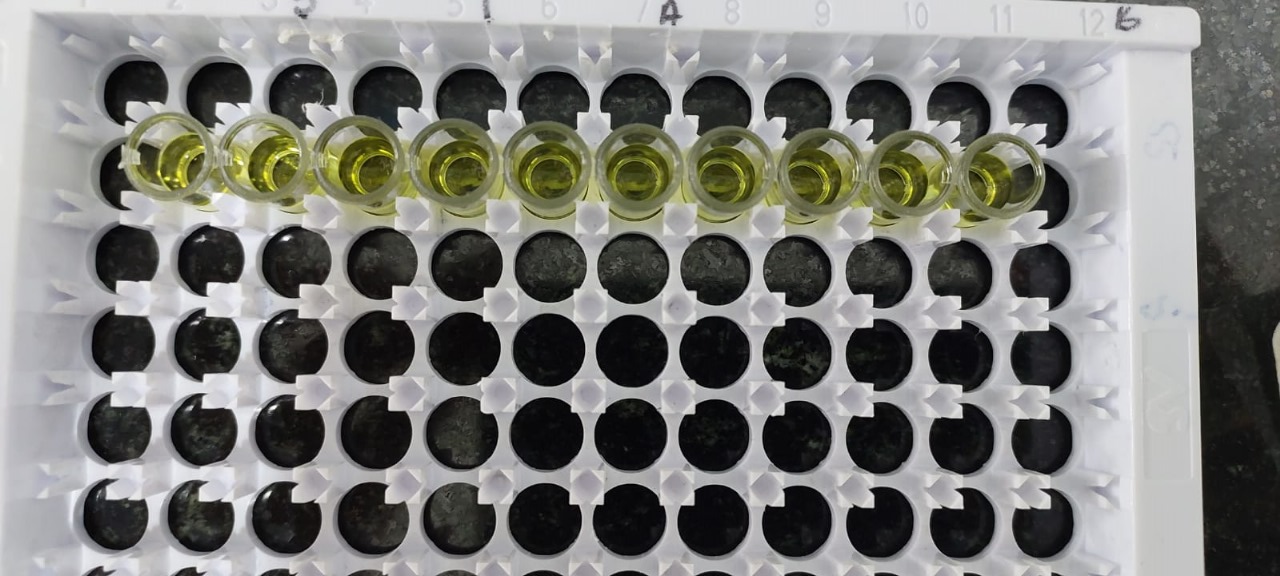
|  |  |  |  |
| --- | --- | --- | --- |
| [**Sample.No**](http://sample.no/) |  | **OD Value** | **pg/ml** |
| **1** | **Control** | **0.159** | **112.9** |
| **1** | **Control** | **0.141** | **100.1** |
| **2** | **P.sativum (100µg)** | **0.1** | **71.0** |
| **2** | **P.sativum (100µg)** | **0.103** | **73.2** |
| **3** | **P.sativum (200µg)** | **0.06** | **42.6** |
| **3** | **P.sativum (200µg)** | **0.07** | **49.7** |

**Table-3:** 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

|  |  |  |
| --- | --- | --- |
| Con | *P.sativum* (100µg) | P. sativum (200µg) |
| 106.5 | 72 | 46.15 |
| 6 | 3 | 2 |



**Figure-5:** 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.

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**Figure-6:** ELISA Analysis Showing Dose-Dependent Inhibitory Effect of *P.sativum* on MMP-9 Concentration.

**Dose-Response Relationship:** There appears to be a dose-dependent inhibitory effect of *pisum sativum on* MMP-9 concentration. As the dose increases from 100 µg to 200 µg, the mean MMP-9 concentration decreases, indicating greater inhibition.

**Precision of Measurements:** The SEM values are relatively low across all groups, indicating that the mean values are precise and reliable.

**Efficacy of *pisum sativum*:** The data suggests that *pisum sativum* is effective in reducing MMP-9 levels, with the higher dose (200 µg) being more effective than the lower dose (100 µg).

# DISCUSSION

Our study highlights the ability of Pisum sativum to significantly reduce MMP-9 concentrations in human dentin in a dose-dependent manner. This finding is particularly relevant in the context of dental procedures, where inflammation and the activation of matrix metalloproteinases (MMPs) are critical factors.Indomethacin, a well-known nonselective COX inhibitor, is frequently used to alleviate pain, fever, stiffness, and swelling associated with inflammatory conditions. By inhibiting the COX pathway, indomethacin effectively reduces inflammation, which is a common feature in numerous human diseases[(Montagner et al., 2014)](https://paperpile.com/c/WJ2rWA/v1va)MMPs are present in various inflammatory diseases and play a crucial role in tissue remodelling and degradation[(Anumula et al., 2024)](https://paperpile.com/c/WJ2rWA/W27S). During dental bonding procedures, acid etching activates these MMPs, which can compromise the integrity of the dental structure. Our findings suggest that the suppression of MMPs by indomethacin may stem from the indole group in its structure, which potentially represses gene transcription related to MMP expression[(Website, n.d.-b)](https://paperpile.com/c/WJ2rWA/4bSo). This mechanism could lead to the inhibition of gelatinolytic degradation, thereby preserving the dentin's structural integrity.Overall, the interaction between Pisum sativum indomethacin presents an intriguing avenue for enhancing dental treatments by mitigating the activation of MMPs, ultimately improving patient outcomes in scenarios where inflammation and tissue degradation are concerns[(Galler et al., 2021)](https://paperpile.com/c/WJ2rWA/tftL). Further research into these compounds could yield significant insights into their combined therapeutic potential.[(Shailendra et al., 2019)](https://paperpile.com/c/WJ2rWA/3IwA)The in vitro assessment of Pisum sativum (pea extract) as an inhibitor of matrix metalloproteinases (MMPs) in human dentin reveals significant potential for its application in dentistry. MMP inhibitors play a vital role in prolonging the lifespan of dental restorations by preventing the breakdown of dentin collagen during adhesive bonding processes.[(de Moraes et al., 2020)](https://paperpile.com/c/WJ2rWA/BDoz)Research has explored a variety of MMP inhibitors, including chlorhexidine and others, to evaluate their effectiveness in enhancing both bond strength and durability of dental restorations. These studies indicate that effective MMP inhibition can significantly improve the performance of dental adhesives, leading to more robust and long-lasting restorations.[(Montagner et al., 2014)](https://paperpile.com/c/WJ2rWA/v1va)Pisum sativum offers a natural alternative to synthetic MMP inhibitors, presenting an exciting opportunity to enhance dental treatments. By potentially stabilizing the collagen matrix within dentin, pea extract may help mitigate the enzymatic degradation that often compromises the integrity of dental bonds over time[(Li et al., 2015)](https://paperpile.com/c/WJ2rWA/DFLc). Further investigations into the mechanisms and efficacy of \*Pisum sativum\* could provide valuable insights, paving the way for its incorporation into dental materials and practices aimed at improving restoration longevity and patient outcomes[(de Moraes et al., 2020)](https://paperpile.com/c/WJ2rWA/BDoz)In this study[(Bhandari et al., 2021)](https://paperpile.com/c/WJ2rWA/OV7g), the results defend that the application of A. vera in the specimens inhibited MMPs activity by plate assay method and gelatin zymography assay with and without dentin bonding agent. In the plate assay method, a zone of hydrolysis was seen around the surrounding area of the right-hand side, a well-containing enzyme source which indicates the enzymatic activity of the human dentin. On the left-hand side well-containing A. vera treated human dentin powder, no such zone of hydrolysis was appreciated.Using Pisum sativum as an MMP inhibitor focuses on inhibiting MMP activity, which is responsible for the breakdown of collagen fibrils in the dentin matrix. By preventing this enzymatic activity, MMP inhibitors like pea extract could potentially preserve the structural integrity of the dentin-adhesive bond over time.[(Li et al., 2015)](https://paperpile.com/c/WJ2rWA/DFLc)Research has demonstrated that MMP inhibitors, including various natural extracts, can notably enhance the bond strength of dental adhesives, particularly following aging simulations that replicate the long-term effects of oral conditions. These studies often employ microtensile bond strength (microTBS) tests to assess the durability of adhesive bonds after exposure to storage or thermomechanical aging under simulated conditions[([No Title], n.d.)](https://paperpile.com/c/WJ2rWA/xyfR).By comparing groups that received treatment with MMP inhibitors to untreated control groups, researchers consistently find that the treated adhesives exhibit improved bond strength and diminished degradation over time[(Bhandari et al., 2014)](https://paperpile.com/c/WJ2rWA/Z4Ub). This enhanced performance is critical, as it indicates that MMP inhibitors can effectively combat the enzymatic activity that often leads to the breakdown of dentin collagen, which is essential for maintaining a strong and durable bond.Furthermore, the use of natural extracts as MMP inhibitors presents an appealing alternative to synthetic options, potentially offering additional benefits such as biocompatibility and reduced toxicity. Ongoing research in this area aims to further elucidate the mechanisms by which these natural compounds contribute to improved adhesive performance and longevity, paving the way for advancements in dental material formulations. This could ultimately lead to more resilient dental restorations that better withstand the challenging conditions of the oral environment, enhancing patient satisfaction and clinical outcomes..[(Mazzoni et al., 2014)](https://paperpile.com/c/WJ2rWA/Y36Y)In studies using different MMP inhibitors, including natural alternatives like pea extract, the results have shown reduced adhesive failures and better preservation of the bond after prolonged exposure to oral-like environments. This suggests that Pisum sativum could be a valuable addition to dental materials aimed at improving the longevity of restorations .[(Almahdy et al., 2012)](https://paperpile.com/c/WJ2rWA/EqDD)Overall, while further studies are needed to fully establish the benefits and optimise the use of Pisum sativum in dentistry, its application as an MMP inhibitor shows considerable potential in enhancing the durability of dental treatments.The in vitro evaluation of Pisum sativum as a matrix metalloproteinase (MMP) inhibitor in human dentin highlights its potential to improve the durability of dental restorations. MMPs, including MMP-2, MMP-8, and MMP-9, are enzymes present in human dentin that degrade collagen in the hybrid layer after adhesive procedures, leading to long-term failure of restorations[(Website, n.d.-c)](https://paperpile.com/c/WJ2rWA/JY4X).MMP inhibitors, including Pisum sativum extracts, are explored for their ability to preserve the structural integrity of the dentin-resin interface by preventing collagen breakdown. Studies show that MMP inhibition can result in better bond stability over time. Common methods to evaluate the effectiveness of MMP inhibitors in human dentin include microtensile bond strength (microTBS) testing, where dentin samples treated with inhibitors are subjected to ageing simulations (e.g., thermomechanical cycles, water storage) and compared with untreated control samples.[(Li et al., 2015)](https://paperpile.com/c/WJ2rWA/DFLc)Natural extracts like Pisum sativum may provide a biocompatible alternative to synthetic inhibitors such as chlorhexidine (CHX). While CHX is effective, its drawbacks, including potential leaching and reduction in bond strength over time, have led researchers to explore alternatives . By applying pea extract as an MMP inhibitor, studies aim to assess whether it can offer stable and long-lasting protection against collagen degradation without the risks associated with synthetic agents.Further research into Pisum sativum’s effectiveness on human dentin is essential, but it's natural, non-toxic profile makes it an attractive candidate for future dental adhesive formulations aimed at improving the longevity of restorations[(Website, n.d.-d)](https://paperpile.com/c/WJ2rWA/QFMl)

# CONCLUSION

To sum up, our in-vitro investigation of pisum sativum’s role as a human dentin matrix metalloproteinase-9 (MMP-9) inhibitor offers important new information about the plant's possible medical uses. The results show that pisum sativum has a significant, dose-dependent inhibitory effect on MMP-9 concentrations, suggesting that it might be a useful substitute for conventional therapies in the modulation of gelatinase activity. This work implies broader applications of pisum sativum in the treatment of MMP-related disorders in addition to demonstrating its effectiveness in improving the integrity of dentin-resin interfaces. Pisium sativum is a versatile food and dietary supplement due to its capacity to suppress MMP activity and perhaps reduce oxidative stress.Furthermore, parallels drawn between our results and the existing literature on the neuroprotective effects of pisum sativum species suggest that pisum sativum may exert beneficial effects not only in dentistry but also in the field of cognitive health and disease management. Since we recommend additional research on the mechanisms underlying the effects of pisum sativum, it is clear that this natural compound gives a perspective to improve the results of teeth treatment and increase the overall health of the oral cavity. Future studies should aim to explore the clinical applications of pisum sativum, such as its incorporation into dental adhesives and its potential role in comprehensive therapeutic strategies for MMP-related dysfunction. By deepening the understanding of pisum sativum treatment characteristics, it can contribute to the development of dental and innovative approaches to improve dental care.

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