



## Efficacy of herbal 1% *Coriandrum sativum* leaves extract mucoadhesive gel as local drug delivery on salivary matrix metalloproteinase -9 levels in the treatment of chronic periodontitis - A clinico-biochemical study

**Running title:** Local drug delivery of 1% *C. sativum* gel

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**Abstract:**

**Background and Objectives:** The pathogenesis of inflammatory periodontal diseases essentially involves degradation of extracellular matrix molecules, and collagen breakdown and matrix metalloproteinases (MMPs) are proteinases primarily involved in this process. Herbal products are the recent advancement in the field of alternative medicines for the management of chronic periodontitis. They can be used as local drug delivery agents over conventional antibiotics because of their extensive natural activity, advanced safety margin, and inferior costs. The aim of this study was to evaluate the anti-inflammatory effects of subgingival application of 1% extract from *C. Sativum* leaves (1% CSG) in gel form, on salivary MMP-9 (sMMP-9) levels in the treatment of chronic periodontitis.

**Subjects and methods:** A randomized, double blinded, split mouth, clinical study was conducted on 23 subjects (n=46 pockets) having moderate chronic periodontitis. The subjects were equally divided into two groups: Test group (n=23 pockets) and control group (n=23 pockets). Post phase one periodontal therapy the test site received 1% CSG, and the other side received a placebo gel. The periodontal parameters; plaque index, sulcus bleeding index, periodontal pocket depth (PPD), and clinical attachment level (CAL) were assessed, and salivary samples were obtained from the patients to assess the sMMP-9 levels using enzyme linked immunosorbent assay (ELISA) at baseline, 1 month, and 3 months.

**Results:** SPSS software analysed all the data by repeated measure analysis of variance, paired t-test, and sample t-test with the difference of  $P < 0.05$ . Both Periodontal parameters and sMMP-9 showed a statistical reduction in the experimental group at 1 month and 3 months of evaluation. Significant better improvement was observed in the experimental group from 1 month to 3 months after the assessment in PPD and CAL.

**Conclusion:** Locally delivered extracts of 1% *Coriandrum sativum* gel was more effective in reducing periodontal clinical parameter and sMMP-9 levels when used as an adjunct to scaling and root planing in the treatment of moderate chronic periodontitis.

**Keywords:** *Coriandrum sativum*, herbal local drug delivery, local drug delivery, matrix metalloproteinase-9

## **Introduction**

Periodontitis is a chronic disease of periodontal tissues which is caused by the initiation of a host inflammatory response by microbiological plaque and infectious bacteria present in the oral cavity. The pathogenesis of periodontitis includes, increase in the production and release of proinflammatory cytokines including interleukin-1, interleukin-6, tumor necrosis factor alpha and matrix metalloproteinases.[1] However, along with killing of the pathogenic microorganism this also results in the destruction of hard and soft tissues of periodontal apparatus resulting in epithelial ulceration, connective tissue destruction, and loss of alveolar bone. Thus, leading to tooth mobility or even tooth loss.[2]

Matrix metalloproteinases (MMPs) belong to the large family of calcium dependent endopeptidases containing Zinc. They have well- characterized structural and catalytic properties, responsible for tissue remodeling, degradation of the extracellular matrix (ECM), provocation of cytokines and activation of osteoclasts.[3] Therefore, for the management of periodontal disease apart of removal of the etiological agents it is essential to modify the host response as well.

The treatment rendered to arrest this inflammatory process includes, non-surgical periodontal therapy like scaling and root planning (SRP). However, many a times the instrument used is not able to access the deeper pockets thus, not able to eradicate the pathogenic microbacteria completely, resulting in the recurrence of these periodontal pockets.[4]

Therefore, to counter this problem along with SRP various adjunctive agents are used inside these deeper pockets where their sustained release would help combat the bacterial destruction to the periodontal tissues.[5] This is called as controlled local drug delivery system for the treatment of periodontitis.[6] Recently, due to increasing incidence of drug-resistant pathogens and toxicity of existing antibacterial compounds, natural phytochemicals (for example, curcumin, coriander, neem,

Aloevera, Babul, Bakul, lemongrass, tea tree oil, and green tea) are being used as an adjunctive agent for the treatment of periodontitis due to their minimal side-effects, and lower costs.[7] *Coriandrum sativum* belongs to Apiaceae family and is known to have anti-inflammatory, analgesic, anti-bacterial, and anti-oxidant activities.[8] Previous studies have proven that Locally delivered extracts of *C. sativum* along with NSPT were effective in reducing periodontal clinical parameter in the treatment of chronic periodontitis.[7, 9] Therefore, the aim of this present study is to evaluate the anti-inflammatory effects of subgingival application of extract from *C. Sativum* leaves (1%) in gel form, on salivary MMP-9 levels in the treatment of chronic periodontitis.

### **Subjects and Methods**

A randomized, double blinded, split mouth, clinical study was conducted to evaluate the anti-inflammatory effect of 1% *Coriandrum sativum* extract gel (1% CSG) in the patients with moderate chronic periodontitis by assessing the salivary MMP-9 levels and by evaluating the periodontal parameters after its subgingival application.

The patients between 35-65 years of age, having moderate chronic periodontitis, periodontal pocket depth (PPD) of 4–6 mm, no history of substance abuse, antibiotic or periodontal therapy in the last six months, drug allergy, or ongoing orthodontic treatment were included in the study. Pregnant and lactating women, smokers and those with systemic disease were excluded. Informed consent was obtained from patients before entering the study, and the study was reviewed and approved by the Institutional Ethics Committee.

A total of 46 pockets (n=23 patients) were randomly divided into two equal groups. The test group (n = 23) received 1% CSG while the control group (n = 23) received a placebo gel. The patients who participated in this study received complete oral prophylaxis, including scaling and root planning (SRP), along with oral hygiene reinforcements on their first appointment. Participants were refrained from using any mouth rinse during the study period. Two weeks later, the participants were re-evaluated and the parameters were recorded, salivary samples were taken and the 1% CSG and

placebo gel was placed with the help of a blunt cannula respectively in the test and control group in case of persistent pocket and the periodontal pack was placed.

Full mouth Periodontal parameters included plaque index (PI),[10] sulcus bleeding index (SBI),[11] Probing Pocket Depth (PPD),[12] and clinical attachment level (CAL)[13]. All the clinical measurements were performed by a single examiner using calibrated periodontal probe.

The collected salivary specimens were then immediately carried to the laboratory where they were stored at  $-80^{\circ}\text{C}$  before the analysis. The patient was again recalled after 1 month and 3 months likewise, the saliva was collected and periodontal parameters were recorded.

### **Preparation of 1% Coriandrum sativum gel**

After intensive in vitro investigations for optimization and stability, the 1% CSG was prepared by commercially available coriander extract oil, according to the “cold technique” as described by Derakhshandeh et al. [14] The prepared gels were packed in autoclaved glass vials and sealed.

### **Saliva Sample Collection and Analysis**

Saliva was collected at baseline, 1 month and after 3 months post treatment from both the groups. All samples were collected by an investigator to ensure consistent procedures.

Unstimulated saliva, which is not contaminated with blood saliva was collected in order to avoid any confounding factors. The saliva was collected using Eppendorf tubes which were then stored at 20 degree Celsius. MMP-9 levels in collected saliva samples were measured via ELISA immunoassay according to the manufacturer’s instructions (R&D Systems Inc., Minneapolis, MN, USA).

SPSS version 17 software (SPSS Inc., Chicago, IL, USA) analysed all the data. Repeated measure analysis of variance, paired t-test, and sample t-test with the difference of  $P < 0.05$  were used for statistical analysis.

### **Results**

This study was conducted on 23 patients (n=46 sites) None of the selected patients dropped out before the termination of the study and the test group showed uneventful healing with no signs of allergy, swelling, or inflammation. This ensures that the material is biocompatible and well tolerated by the patients.

The patients of both the groups maintained their oral hygiene well as reflected by the periodontal parameters. The intergroup comparison regarding the full mouth periodontal parameters revealed no statistically significant differences ( $P > 0.05$ ) signifying similarity in the oral hygiene in the patients of both the groups. The mean reduction in PI (test group from 2.42 to 0.72 and control groups from 2.11 to 1.12) and SBI (test group from 2.32 to 0.62 and control groups from 2.65 to 1.30) was noted during the study period as seen in Figure 1. However, the test group demonstrated better control than the control group in both the aspects. Remarkable improvement was seen in all the groups regarding the site-specific periodontal parameters (PPD and CAL) from baseline to 3 months in all the groups which can be seen in the intragroup comparison ( $P < 0.001$ ). (Graph 1) Intergroup comparison reveals statistically significant difference from baseline to one month, where test group performed better, however, no difference was observed when comparison was made from 1 month to 3 months. The P value obtained between baseline and 3 months showed a statistical difference, i.e.,  $P \leq 0.05$  was observed. (Table 1) The alterations in the level of MMP-9 were not statistically significant in intergroup comparison during the study period. However, intragroup comparison demonstrated significant reduction in sMMP-9 levels. (Graph 2)

## **Discussion**

Periodontitis is a disease which is considered to have multifactorial etiology including, periodontopathic bacteria, systemic factors, environmental factors and host response to it. Various studies have reported that in response to these periodontopathic bacteria, host releases various enzymes which includes matrix metalloproteinases, that causes killing of these bacteria along with destruction of periodontal connective tissue and resorption of alveolar bone.[15,16] Therefore,

eradication of periodontal bacteria along with regulation of host response is considered to be the primary treatment strategy for the management of periodontal disease.[17]

MMP-9 which is derived from polymorphonuclear leukocyte (PMN) and periodontal pathogens is considered to be one of the main proteinases related to tissue destruction and remodeling events in periodontal diseases. The patients suffering from periodontitis is reported to have significantly higher salivary MMP-9 levels as compared to healthy controls. [2,18] Our study is in accordance with these findings as the salivary MMP-9 levels were higher at the baseline and they subsequently decreased within three months, when the treatment was rendered.

Local application of drugs has various advantages over systemic administration which includes, decrease chances of antibiotic resistance, lower systemic side effects as they target site specific bacterial agents and its toxic products.[19] In the present study also, the test group showed better results and there was no side effect reported by any of the subject.

Various drug delivery systems are available now a days for example irrigational, injectable systems, gels, strips and compacts, fibers, film, vesicular systems, microparticle system, and nanoparticle system.[20] In the present study, we have used 1% CS mucoadhesive gel which was further covered by periodontal dressing to retain the LDD agent at the test site.

According to Silva *et al.*,[21] and Fulbel *et al.*,[22] *C. sativum* has potent antibacterial action against the Gram-negative bacteria. A recent *in vivo* study showed that *C. sativum* causes Propidium iodide incorporation in the bacterial cell which results in concomitant loss of bacterial cellular functions which includes efflux activity, respiratory activity and membrane potential resulting in cell membrane damage, and cell death. It also contains Aliphatic (2E)-alkenals and alkanals which have shown to possess anti-bacterial properties. [23]

Previous studies have reported that the presence of effective antioxidant profile in *Coriandrum sativum* due to high total phenolic content. This causes 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity, lipoxygenase inhibition, phospholipid peroxidation inhibition, iron chelating activity, hydroxyl radical scavenging activity, superoxide dismutation, glutathione reduction and antilipid peroxidation. [24]

Our study is in accordance with the aforementioned as, a considerably sound reduction in plaque and the sulcus bleeding score was obtained in the test group. Also, PPD and CAL were found to be significant in intragroup comparison in the test group during 1–3 months, indicating excellent antibacterial and anti-inflammatory effects demonstrated by *C. sativum*.

Several periodontal bacteria together with microbial proteases such as metalloproteases including host-derived MMPs, all participate in the process leading to progression of periodontitis, tissue, and ligament degradation. MMP-9 is among the best studied proteinases when it comes to its role in periodontitis and its activation in infections. Elevated activity of gelatinases MMP- 9 has also been found

in saliva from chronic periodontitis patients. [25,26] Thus, in the present study, we decided to use unstimulated salivary samples that were obtained from patients diagnosed clinically with chronic periodontitis at baseline and post treatment to check for the variation in the MMP-9 levels post periodontal therapy.

According to Nair et al,[27] *C sativum* effectively causes the reduction in Serum tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-6, IL-1  $\beta$  levels, and peritoneal macrophage expression. Various other studies have also reported that *Coriandrum sativum* caused depression in the pro-inflammatory cytokines expression and further reducing the enzymatic activation.[28,29,30] Our study is in accordance with these finding as a significant reduction was seen in our study in the salivary MMP-9 levels post treatment in both the groups.

## **Conclusion**

The finding of the present study is significant and confirms the use of *Coriandrum sativum* in treating periodontal diseases. However, clinical trials with longer duration and larger study sample are required to confirm the findings.



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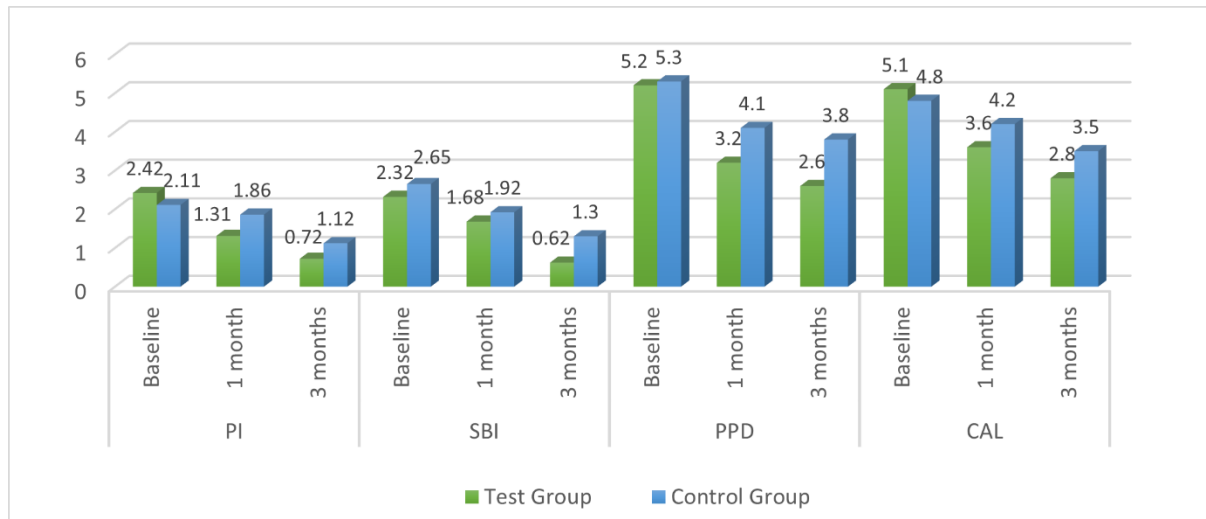
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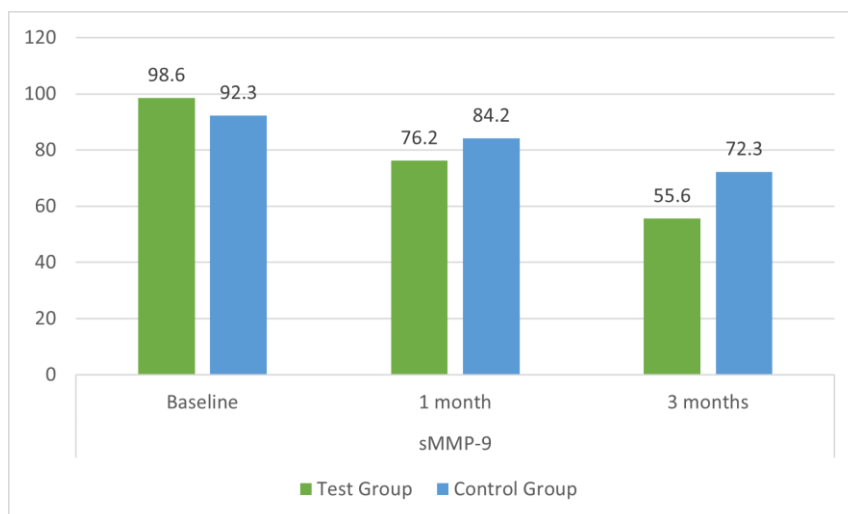
Extracts from the aerial part of *Coriandrum sativum* has anti-inflammatory properties.

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### Tables and Graphs with legends



**Graph 1:** The mean reduction in plaque index (PI), sulcus bleeding index (SBI), Probing Pocket Depth (PPD), Clinical Attachment Level (CAL) as observed in the test and control groups at baseline, 1 month, and 3 months



**Graph 2:** The mean reduction in salivary Matrix metalloproteinase-9 levels (sMMP-9) as observed in the test and control groups at baseline, 1 month, and 3 months

**Table 1:** Intergroup comparison of PI-Plaque Index, SBI- Sulcus Bleeding Index, PPD- Probing Pocket Depth, CAL- Clinical Attachment Level, sMMP-9- Salivary Matrix Metalloproteinase-9 Levels

Parameters	PI		SBI		PPD		CAL		sMMP-9	
	Mean SD	P	Mean SD	P	Mean SD	P	Mean SD	P	Mean SD	P
Baseline to 1 month	-0.86 ±0.12	0.76	-0.09 ±0.14	0.92	-0.8 ±0.12	0.87	-0.9 ±0.11	0.77	-18.9 ±0.21	0.21
Baseline to 3 months	-0.71 ±0.11	0.01*	-0.35 ±0.10	0.01*	-1.1 ±0.22	0.015*	-01 ±0.21	0.001	23.0 ±0.14	0.13

- Denotes statistical significance obtained  $\leq 0.05^*$