



Effect of topical aloe vera gel on gingival crevicular fluid interleukin-1 beta and interleukin-17 levels in patients with chronic periodontitis; A double-blind split-mouth randomized clinical trial

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Abstract

Introduction: Cytokines play a prominent role in the induction of periodontal diseases. Aloe vera can ameliorate periodontal disease considering its anti-inflammatory and antibacterial effects.

Objectives: This study investigated the effect of topical aloe vera gel, associated with scaling and root planing (SRP), on interleukin-1 (IL-1) and interleukin-17 (IL-17) of gingival crevicular fluid (GCF) levels in chronic periodontitis patients.

Patients and Methods: This study recruited 20 patients diagnosed with moderate to severe chronic periodontitis (with probing pocket depths of ≥ 5 mm). The control group subjects underwent only SRP; the test group subjects underwent SRP, followed by topical aloe vera gel application. Periodontal clinical parameters, including probing depth (PD), clinical attachment level (CAL) and gingival index (GI), were determined; GCF levels of IL-1 and IL-17 were determined using the enzyme-linked immunosorbent assay (ELISA) at baseline and one month postoperatively.

Results: There were significant decreases in periodontal clinical parameters in both groups compared to the baseline. The test group exhibited a significant decrease in interleukin levels compared with the control group as follows; interleukin-1 beta (IL-1 β) (control; 61.78 ± 14.54 , test; 43.06 ± 10.99 ng/mL) ($P < 0.001$), IL-17 (control; 81.33 ± 16.66 , test; 57.04 ± 16.26 ng/mL) ($P < 0.001$).

Conclusion: Topical aloe vera gel in combination with SRP significantly improved clinical parameters of periodontitis and decreased IL-1 β and IL-17 GCF levels.

Trial Registration: The trial protocol of the present study was approved by the Iranian registry of Clinical Trials (identifier: IRCT20100412003690N11; <https://en.irct.ir/trial/44975>; ethical code #IR.TBZMED.REC.1398.1113).

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Introduction

Chronic periodontitis is an infectious condition causing inflammation in the tooth-supporting tissues, progressive loss of attachment and bone loss. The periodontal pocket formation is a frequent consequence of this disease process, except in the case of gingival recession with loss of attachment (1). The main cause of chronic periodontitis is plaque accumulation on tooth surfaces. Loss of attachment and bone mass is associated with an increased proportion of gram-negative bacteria in the subgingival plaque and an increased count of bacteria known as periodontal pathogens or the “red complexes.” These microorganisms can synthesize products such as collagenase, hyaluronidase and proteases, damaging bound and epithelial cells (1).

Key point

This study evaluated the post-therapeutic clinical parameters and cytokine levels in gingival crevicular fluid (GCF) in patients with moderate to severe chronic periodontitis, receiving mechanical therapy alone or mechanical therapy in association with local aloe vera gel.

A lack of equilibrium between the periodontal tissue destruction by periopathogenic bacteria in dental plaque and repair triggers a chronic inflammatory disease referred to as periodontitis. Cells in periodontal fibers can recognize these bacterial pathogens that induce pro-inflammatory cytokines, systemic inflammatory responses, tissue-damaging enzymes and chemokines. Cytokines play a



prominent role in the induction of periodontal diseases. The primary cytokines with a role in chronic periodontal diseases are interleukin-1 (IL-1), IL-6, IL-8, IL-10, IL-17 and interferon (INF), which affect the activity of immune cells (2).

Since plaque accumulation is the first factor in the onset of periodontal breakdown, any factor that prevents plaque formation and consequently, microorganisms can improve the disease or slow its progression (1). Therefore, systemic antibiotic therapy (like azithromycin and clarithromycin), topical antibiotic therapy and lasers with or without scaling and root planing (SRP) can slow the course of chronic periodontitis and improve the disease (3).

Studies have shown that aloe vera contains ingredients with anti-inflammatory effects. For example, bradykinase is an enzyme found in aloe vera that reduces skin inflammation. Fatty acids called salicylic acid and hormones called auxins and gibberellins can also reduce inflammation. These anti-inflammatory agents often stimulate the immune system and collagen growth or block inflammatory pathways (4). Another potent active ingredient in aloe vera is anthraquinones, with a function similar to tetracycline; inhibition of bacterial protein synthesis through blocking the ribosomal entry site for the amino acid tRNA (5).

Aloe vera is one of the most famous natural remedies and can reduce swelling and redness. In previous study found that aloe vera extract decreased inflammation in an inflammatory model of injection-induced arthritis in rats by 48% (6). Furthermore, aloe vera affects periodontal diseases, according to some studies. Bhat et al examined the clinical effects of aloe vera gel during periodontal surgeries in patients with periodontal disease after mechanical debridement, reporting that topical aloe vera gel improved periodontal status; therefore, it can be used as a topical drug in periodontal pockets (7).

Pradeep et al studied the clinical effects of topical aloe vera gel, in association with SRP, in patients with type 2 diabetes mellitus and chronic periodontal disease, reporting that patients in the aloe vera group exhibited significant decreases in plaque index and probing depths (PDs) compared to the placebo group. In addition, the clinical attachment level (CAL) increased from baseline to the 3-month postoperative interval (8). Vangipuram et al reported the positive effect of aloe vera and chlorhexidine (CHX) mouthwash on the periodontium; therefore, it might be an alternative product to treat and prevent gingivitis (9).

Kurian et al examined the efficacy of 1% topical metformin and aloe vera gel as an additional therapy with SRP in treating intraosseous defects in chronic periodontitis. They concluded that all indicators, such as gingival index (GI), bleeding on probing (BOP), PD, and CAL, ameliorated in all the study groups. However, the mean PD reduction, the CAL gain, and the bone fill percentage were higher in the metformin and aloe vera

groups compared to the placebo group (10).

Objectives

Since limited data are available on the aloe vera local effects in periodontal pockets in periodontal disease patients and none of these studies have assessed cytokine levels, this study investigated the topical aloe vera gel's effect on crevicular fluid IL-1 and IL-17 levels in patients with chronic periodontitis.

Patients and Methods

Study design

The present double-blind, randomized, split-mouth study was conducted in 2015–2016 in Tabriz, Iran. Twenty patients diagnosed with moderate to severe chronic periodontitis, aged 35–50 years, were recruited from those referred to the Department of Periodontics, Faculty of Dentistry. All the participants signed informed written consent forms.

Inclusion criteria

Patients with moderate to severe chronic periodontitis with at least four teeth with a PD of ≥ 5 mm in similar quadrants (the upper or lower jaw).

Exclusion criteria

Patients with a history of alcohol abuse, current smokers, systemic diseases such as diabetes, systemic or topical antibiotic therapy or over-the-counter antioxidants such as vitamin C and vitamin E in the past three months, known hypersensitivity to aloe vera, exclude from the study. Other exclusion criteria were pregnant and nursing mothers and also patients undergoing orthodontic treatment, having endodontic and periodontal combined lesions, periapical lesions and severe tooth decay.

The oral cavity was allocated to two case and control quadrants, using a randomized block for each patient. SRP was conducted routinely in the case quadrant, with two teeth randomly selected as a test group and the two other teeth served as a control group in the contralateral quadrant. The clinical parameters of PD, CAL and GI were assessed in the mesiobuccal, buccal, distobuccal and lingual areas in each tooth. PD, CAL and GI were considered secondary outcomes. The PD was determined by measuring the distance from the gingival margin to the bottom of the pocket. CAL was defined as the distance from the cemento-enamel junction to the bottom of the pocket, according to UNC-15 probe. Meanwhile, the Loe and Sillness index was conducted to determine the GI (11). In addition, IL-1 and IL-17 levels, as primary outcomes, were analyzed by an enzyme-linked immunosorbent assay (ELISA) test. An experienced periodontist blinded to the treatment protocols clinically examined all the subjects. Five patients were examined in a similar manner every one hour to determine intra-examiner reliability, which indicated that >95% of the records were within 1 mm.

Cotton rolls were utilized to isolate the examined sites. Then, the saliva and supragingival plaque were removed. A #25 paper point was placed in the gingival sulcus of each pocket and removed after four minutes to collect baseline samples, followed by placing the paper point in a test tube containing normal saline solution, which was stored in a box containing dry ice at 20°C to transfer to the laboratory. All the participants underwent full-mouth subgingival and supragingival SRP using an ultrasound device and periodontal curettes without time limit. All the patients were provided with standard oral hygiene instructions.

An insulin syringe was used in the test group to inject the aloe vera gel into the gingival pocket from the bottom of the pocket to the gingival margin. Concerning the contralateral control teeth, the entire procedure was carried out as in the previous group, except that distilled water was employed instead of aloe vera gel. The treated areas were then carefully covered with a cyanoacrylate bandage to keep the material in the pocket. The patients were asked to refrain from brushing or flossing the treated areas, avoid hard or sticky foods and not touch the area with their tongue or fingers. Clinical parameters such as GI, PD and CAL were determined with a UNC-15 probe (UNC-15, Hu-Friedy, Chicago, IL, USA) and repeated after 30 days.

Preparation of the aloe vera gel

Peeled aloe vera leaves were first washed with sterile water and then immersed in a suitable bactericidal and antifungal solution, such as a microphone, for 5–10 minutes. The gel was separated from the leaves by carefully plucking the outer green peel. The separated matrix gel was prepared by dissolving it in a solution to homogenize and separate the intermediate fibers included in the gel extraction process. The gel was stabilized by adding a non-toxic oxidizing agent. For catalytic oxidation, non-toxic oxidizing agents such as hydrogen peroxide were selected and added after distillation then heating for 30 minutes until the solution had a clear appearance. The clear appearance indicated the completion of the oxidation process. The gel was transferred to a sterilized 50-phantom vial under a ventilated incubator (12).

Analysis of interleukins

The samples' IL-1 and IL-17 levels were determined through an enzyme-linked immunosorbent assay (Mybiosource, Vancouver, Canada, catalog number IL-17: mbs7640761, IL-1; mbs017881) following the manufacturer's instructions. The samples were stored at ambient temperature (18–25°C) before the tests.

Statistical analysis

The data were analyzed with SPSS version 20 (SPSS Inc., IL, Chicago, USA). Descriptive statistics were conducted that included means, standard deviations and frequencies. The normal distribution of the data was checked by the

Kolmogorov-Smirnov test. The normal distribution of all the variables is mandated using parametric tests. Therefore, the paired *t* test was used to determine the changes in the variables after treatment (intra-group). An independent *t* test was conducted to compare the control and aloe vera groups (inter-group). Statistical significance was set at $P \leq 0.05$.

Results

Twenty participants (9 men and 11 women, aged 35-50 years; mean age; 43.7 years) were recruited for the study. Table 1 presents the levels of PD, CAL, GI, IL-1 and IL-17 in the subjects at baseline and 30-day postoperative interval. In the aloe vera group, the mean PD decreased from 4.82 ± 0.82 mm at baseline to 2.13 ± 0.64 mm after treatment ($P \leq 0.05$). Before treatment, no significant difference was noted in PD between the two group subjects. However, the PD in the aloe vera group subjects decreased significantly after treatment compared to the control group ($P = 0.038$).

In the aloe vera group subjects, the mean CAL decreased from 3.89 ± 0.40 mm at baseline to 1.82 ± 0.375 mm after treatment ($P \leq 0.05$). No significant difference was noted in CAL between the two group subjects before treatment. However, the CAL in the aloe vera group subjects decreased significantly after treatment compared to the control group ($P = 0.046$).

In the aloe vera group subjects, the mean GI after treatment decreased from 2.23 ± 0.34 before treatment to 1.39 ± 0.18 ($P \leq 0.05$). Before treatment, no significant difference was detected in GI between the two group subjects. After treatment, the GI in the aloe vera group subjects decreased significantly compared to the control group ($P = 0.042$).

The IL-1 level in the aloe vera gel group before treatment was 75.93 ± 15.5 ng/mL, which decreased to 43.06 ± 10.99 ng/mL after 30 days. Paired *t* test showed a significant decrease in the IL-1 level in the aloe vera gel group subjects after treatment. A comparison of the two groups before treatment showed no significant difference in IL-1 levels. However, after treatment, IL-1 levels in the aloe vera gel group subjects decreased significantly compared to the control group subjects ($P \leq 0.001$).

An analysis of IL-17 levels showed that in the aloe vera gel group subjects, the pre-treatment interleukin level was 109.59 ± 22.44 ng/mL, decreasing to 57.04 ± 16.26 ng/mL 30 days after treatment ($P < 0.001$). The paired T-test showed that the IL-17 level decreased significantly after treatment in the aloe vera gel group subjects ($P < 0.001$). A comparison of the two groups before treatment showed no significant difference in IL-17 levels (p-value: 0.830). After treatment, IL-17 levels in the aloe vera gel group decreased significantly compared to the control group ($P < 0.001$).

At baseline, the test and control groups exhibited similar profiles concerning PD, CAL, GI, IL-1, and IL-17 levels ($P > 0.05$). After 30 days, PD, CAL, and GI decreased

Table 1. Comparison of clinical and biochemical parameters at baseline and 30 days after treatment in test and control groups

Parameters		Test		Control		
		Mean \pm SD	<i>P</i> value*	Mean \pm SD	<i>P</i> value*	<i>P</i> value**
PD (mm)	Baseline	4.82 \pm 0.82	0.001	4.67 \pm 0.82	0.001	0.683
	After 30 days	2.03 \pm 0.49		2.46 \pm 0.57		0.038
CAL (mm)	Baseline	3.89 \pm 0.40	0.001	3.64 \pm 0.49	0.001	0.155
	After 30 days	1.82 \pm 0.37		2.25 \pm 0.47		0.046
GI	Baseline	2.23 \pm 0.34	0.001	2.0 \pm 0.54	0.001	0.293
	After 30 days	1.39 \pm 0.18		1.53 \pm 0.30		0.042
IL-1 β (ng/mL)	Baseline	75.94 \pm 15.56	<0.001	78.52 \pm 14.97	0.043	0.658
	After 30 days	43.06 \pm 10.99		61.78 \pm 14.54		<0.001
IL-17 (ng/mL)	Baseline	109.59 \pm 22.44	<0.001	107.82 \pm 20.66	0.038	0.830
	After 30 days	57.04 \pm 16.26		81.33 \pm 16.66		<0.001

PD, Probing depth; CAL, Clinical attachment level; GI, Gingival index; IL-1 β Interleukin-1 β ; IL-17: Interleukin-17.

* Intra-group analysis, ** Inter-group analysis.

significantly in both groups compared to baseline ($P < 0.001$). The improvements in the tested clinical parameters in the aloe vera group were significantly greater 30 days after treatment compared to the control group ($P < 0.05$; Table 1).

The concentrations of IL-1 and IL-17 in the control group decreased significantly from the baseline values (IL-1 β : 78.52 \pm 14.97; IL-17: 107.82 \pm 20.66 ng/mL) up to 30 days after treatment (IL-1 β : 61.78 \pm 14.54; IL-17: 81.33 \pm 16.66 ng/mL; $P < 0.001$). In the test group, IL-1 and IL-17 levels decreased significantly from the baseline value (IL-1 β : 75.94 \pm 15.56; IL-17: 109.59 \pm 22.44 ng/mL) up to 30 days after treatment (IL-1 β : 43.06 \pm 10.99; IL-17: 57.04 \pm 16.26 ng/mL; $P < 0.001$). After treatment, IL-1 and IL-17 levels in the aloe vera gel group decreased significantly compared to the control group ($P < 0.001$).

Discussion

Periodontitis is an inflammatory condition leading to the loss of connective tissue and alveolar bone. Various environmental and genetic factors induce the occurrence and prognosis of periodontitis, particularly the molecules associated with the host's immune response, such as inflammatory cytokines (13). Aloe vera has antibacterial properties and contains compounds effective in reducing swelling and pain and accelerating wound healing (13,14). In this context, the present study investigated the effect of topical aloe vera gel on IL-1 and IL-17 levels in gingival crevicular fluid (GCF) in patients with chronic periodontitis.

The design of this split-mouth study allowed local aloe vera gel to be transferred to other areas, resulting in systemic effects; however, studies have shown that gingival fluid and saliva are separate entities. Therefore, studies with a split-mouth design have many advantages that allow paired groups to be compared. In the present study, a significant improvement in clinical parameters was observed in both groups. Given the mechanical debridement in both groups, these results are not unexpected. However, most of the changes in periodontal indices (PD, CAL and GI) were

observed in the aloe vera group.

Hudwekar et al (13) investigated the effect of aloe vera extract on wound healing after periodontal surgery in chronic periodontitis, reporting a significant effect of aloe vera extract on wound healing in the first week of surgery. Kurian et al (10) evaluated the effect of topical 1% metformin and aloe vera gel as adjunctive therapy to SRP in treating intraosseous defects in chronic periodontitis. According to the results, SRP+aloe vera gel improved parameters such as GI, BOP, PD and CAL, similar to the SRP+1% metformin gel.

Altincik et al showed that aloe vera positively affected gingivitis (15). Furthermore, Chandrahas et al (16) showed that the effect of aloe vera mouthwash on gingivitis was similar to 0.2% CHX. They also compared with the test group (distilled water), the modified GI and bleeding index decreased significantly. Vangipuram et al (9) studied the effects of aloe vera and CHX mouthwashes on periodontal health and showed that aloe vera, as a herbal product, was as effective as CHX. They study used the GI to determine the periodontal tissue status in terms of the symptoms of inflammation: swelling, redness, and bleeding (17). According to the results, a significant reduction in the GI was associated with reduced inflammatory markers in the case group. In this study, the GI was similar in the CHX and aloe vera groups. Therefore, it might be administered to treat and prevent gingivitis. The results of the above studies are all consistent with the present study.

Previously Nagireddy et al (18) observed that the IL-17 level in the GCF of patients with chronic periodontitis was significantly higher. Moreover, they found the IL-17 level was directly related to the rate of periodontal degradation and was a good indicator of this disease. IL-1 is a pro-inflammatory cytokine that plays a vital role in the pathogenesis of periodontal disease and bone loss (19,20). It also increases collagenase production by periodontal ligament fibroblasts. Therefore, high interleukin levels in the saliva of patients with chronic periodontitis indicate the role of this cytokine in the development of periodontal inflammation (21).

These findings are consistent with the present study. In this study, 30 days after treatment, IL-1 and IL-17 levels were significantly lower than before, suggesting that the inflammatory factors released from host cells in response to bacteria in the gingival tissue played an essential role in the destruction of periodontal tissues. Aloe vera increases the body's antioxidant capacity by increasing the activity of antioxidant enzymes and reducing lipid oxidation and pro-inflammatory factors (22). In addition, aloe vera inhibits the cyclooxygenase pathway, decreasing the production of prostaglandin E2 (PGE2) from arachidonic acid (23). The stimulating effect of aloe vera on the humeral and cellular immune responses is mediated by the activation of macrophages to produce nitric oxide and secrete cytokines (e.g., IL-1, IL-6 and IFN- α) (24).

Recently, Hai et al, studied burn wound healing in mice and demonstrated that aloe vera paste significantly reduced the production of the inflammatory factors tumor necrosis factor- α (TNF- α) and IL-1 (25). Akgun et al showed significant changes in malondialdehyde, glutathione, myeloperoxidase, TNF- α and IL-1 in wound healing under the effect of aloe vera extract (14). In addition, based on the present study, it is recommended to evaluate the effect of aloe vera on changes in interleukins in longer follow-ups as well as on changes in other interleukins after treating patients with chronic periodontitis.

Conclusion

According to this study, topical aloe vera gel in combination with SRP resulted in further reduction of IL-1 β and IL-17 in the GCF of patients with chronic periodontitis, improving all the periodontal parameters, including PD, CAL and GI.

Limitations of the study

The main limitation of the current study was its short-time follow-up; thus, it is recommended to conduct research with 6-month or 12-month follow-ups.

Authors' contribution

Conceptualization: Masoumeh Faramarzi.

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Writing—original draft: Azin Khorramdel.

Writing—review and editing: Masoumeh Faramarzi and Mehrnoosh Sadighi.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research was conducted in accordance with the tenets of the

Declaration of Helsinki. The Ethics Committee of Tabriz University of Medical Sciences approved this study (Ethical code #IR.TBZMED.REC.1398.1113). Accordingly, written informed consent was taken from all participants before any intervention. Besides, the trial protocol was approved by the Iranian Registry of Clinical Trial (identifier: IRCT 20100412003690N11; <https://en.irct.ir/trial/44975>). Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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