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Original Article

Evaluation of the Effect of Topically Applied Resveratrol Gel as Adjunctive Treatment for Periodontitis

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Abstract

Objective Our objective was to evaluate the impact of topically applied resveratrol (RES) gel as adjunctive to conventional periodontal therapy on both clinical periodontal parameters as well as to assess interleukin-1β (IL-1β) level in gingival crevicular fluid (GCF) in patients with stage I and II grade A periodontitis.

Materials and Method This study was performed on 40 cases aged from 26 to 47 years with means of (37.02 ± 6.88) of both sexes (16 females and 24 males) with stage I and Π grade A periodontitis. They were divided into two groups: group I consisted of 20 cases with stage I and II grade A periodontitis who were treated only with conventional periodontal care (scaling and root planning [SRP]), and group Π consisted of 20 cases with stage I and II grade A periodontitis who were subjected to conventional periodontal therapy (SRP) in conjunction with intrapocket RES gel application. At baseline, 3 months, and 6 months following therapy, all patients had clinical evaluation using gingival index (GI), plaque index (PI), probing pocket depth (PPD), and clinical attachment level (CAL). Also, an enzyme-linked immune-sorbent assay-based biochemical analysis of IL-1β was conducted at baseline, 3 months, and 6 months.

Results Clinical findings were different significantly as correlated within the same group; however, there was no significant difference between both groups. Biochemical evaluation of IL1β revealed no significant variation at baseline and 3 months between both groups, while there was a significant difference during treatment at 6 months.

Conclusion Our findings indicate that RES as supplementary in addition to conventional periodontal therapy may improve periodontitis through anti-inflammatory effects.

Keywords
- topically resveratrol
- adjunctive treatment
- IL-1β
- periodontitis

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Introduction

Periodontitis is regarded as one of the frequent chronic inflammatory diseases by pioneers of periodontology. It is characterized by destruction of all periodontal tissues and is caused by dysbiosis of resident microbiota.[1]

The illness is caused by complicated dynamic interactions between harmful host immune reactions and certain bacterial infections, in addition to environmental variables including smoking.[2]

Periodontitis is classified as a mixed infection due to its pathophysiology, which is distinguished by increased levels of proinflammatory mediators produced in reaction to bacterial biofilms.[3] Elevated serum levels of systemic inflammatory markers have been linked to periodontitis, according to clinical data.[4]

There is increasing evidence that patients with periodontitis may be at risk for developing several systemic illnesses due to systemic inflammation. Moreover, the gingival crevicular fluid (GCF) is the main target of bacteria and leads to the accumulation of inflammatory mediators (interleukin-2 [IL-2], interleukin-6 [IL-6], IL-1β) and microbial endotoxin in the GCF in periodontal disease patients.[5]

Proinflammatory mediators, including IL-1β, have been found to be related to the progression of periodontal disease and the resorption of alveolar bone. It has also been found that GCF cytokine levels decrease after early periodontal treatment.[6] These mediators initiate a series of events that, in certain cases, ultimately result in permanent deterioration of bone structures and subsequent loss of periodontal attachment.[7]

The conventional approach, which consists of scaling and root planning (SRP), has several drawbacks when used in instances that involve inaccessible regions, severe periodontitis, or deep periodontal pockets.[8] As a result, several pharmacological supplementary therapies have been evaluated in an effort to enhance their efficacy. For use in medical therapy, natural products are attracting great interest as an alternative to synthetic substances. Dietary elements produced from plants, such as polyphenols found in a variety of herbs and foods, are advantageous to human health and contribute significantly to disease prevention.[9]

A dietary antioxidant polyphenol, resveratrol (RES; trans-3,4′,5-trihydroxystilbene), is present in various plants, including red wine, grapes, peanuts, and berries.[10] Its antioxidant, anti-inflammatory, and chemopreventive properties have been investigated.[11] In addition to promoting osteogenesis by its direct impact on bone formation,[12] RES also has antibiofilm and antibacterial activity by targeting inflammatory and adhesive markers.[5]

Consequently, it can be hypothesized that RES might be an effective component in supplemental therapy for periodontitis. Animal studies have evaluated the effects of RES administration on experimentally induced periodontitis, showing promising results. However, studies investigating this issue in humans are scarce.[13]

Our objective was to assess the clinical effect of topically applied RES gel, in addition to the biochemical assessment of IL-1β level in GCF as adjunctive to conventional periodontal therapy of stage I and II grade A periodontitis.

Materials and Methods

Study Design

This study was performed on 40 cases aged 26 to 47 years with means of (37.02 ± 6.88) of both sexes (16 females and 24 males) with stage I and Π grade A periodontitis. Every case was chosen from the patient population that attended the outpatient clinic at the Oral Medicine and Periodontology Department, Faculty of Dentistry, Al-Azhar University, Assiut Branch. Every patient who participated in the research had a clinical evaluation. All participants were provided with comprehensive information on the characteristics, possible advantages, and risks of their involvement in the research. The study received approval from the ethics committee of the Faculty of Dentistry, Al-Azhar University, Assiut Branch (no: AUAREC202300008-08). Written permission was obtained from all patients.

Inclusion Criteria

1. In accordance with the American Dental Academy's general guidelines for sending patients to specialists and other treatment settings, it is imperative that all patients do not suffer from any systemic disorders.[14]
2. All cases with stage I and II grade A periodontitis included in the study were in accordance with the criteria of the 2017 classification system, with probing pocket depth (PPD) not more than 5 mm and CAL ranging from 1 to 4 mm.

Exclusion Criteria

- Patients who had been on an antibiotic, immunosuppressive, anti-inflammatory, or antioxidant drug regimen within the 6 months preceding the beginning of the study were excluded.
- Smokers as well as pregnant or lactating women were excluded from the study.
- Patients who had undergone periodontal treatment within the 6 months prior to the study were excluded.

Patients Grouping and Randomization

Cases were randomly allocated by coin flipping into two groups:

- Group I: Twenty patients with stage I and II grade A periodontitis who were treated only with conventional periodontal care (SRP).
- Group Π: Twenty patients with stages I and II grade A periodontitis were subjected to conventional periodontal therapy (SRP) in conjunction with intrapocket RES gel application.

Sample Size Calculation

A power calculation was performed to determine the sample size. The sample size was calculated using ($\alpha = 0.05$) and 85% power. A value of 1 mm was used, with clinical attachment level (CAL) change defined as the primary outcome variable. The minimum clinically significant value considered was

1 mm. It was determined that a minimum sample of 18 patients per group (36 patients in total) would be required. To compensate for sample loss, 40 patients were enrolled in this study.

Resveratrol Oral Gel Preparation

Under stirring, 10 g of 85% glycerol and 5 g of sodium carboxymethyl cellulose were dissolved in 85 g of deionized water to produce the gel at the Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University, Assuit Branch. A 0.01% weight-in-volume solution of RES was prepared by dissolving it in deionized water. Following that, while stirring and in the absence of light, 1 g of this aqueous solution was mixed with 10 g of the vehicle gel. Storage conditions for the vehicle gel and the gel containing RES were 4°C.[15]

The prepared RES gel was supplied as a syringe of gel, with special needles that are designed for the application of gel inside the periodontal pocket.

Periodontal Intervention

Phase I periodontal treatment was provided to all patients. SRPs of the whole mouth were conducted without the addition of disinfectants, a procedure performed using a combination of Gracey curettes (Hu-Friedy, Chicago, United States) and an ultrasonic device (Minipiezon, EMS [Electro Medical System], Le Sentier, Switzerland).

Intrapocket Application of Resveratrol Gel

First areas of application of the highest pocket depth were isolated by cotton roll. The application process started by introducing the needle to the base of the periodontal pocket. Subsequently, the gel was placed as the needle was moved upwards, reaching the gingival edge. After application, patients were asked to refrain from cleaning and flossing their teeth for 4 hours and from drinking, eating, and spitting for 1 hour. Plaque management regimens were also prescribed to patients, and oral hygiene instructions were delivered with each session. In addition, the therapy did not involve the prescription of antibiotics or anti-inflammatory medicines posttreatment. The application was repeated once weekly for 1 month (►**Fig. 1**).

Evaluation of Periodontal Status

Clinical Evaluation

Utilizing the subsequent measures, the periodontal condition of every patient was assessed at baseline, 3 and 6 months subsequent to treatment:

- Gingival index (GI).[16]
- Plaque index (PI).[17]
- PPD as the distance from the free gingival margin to the base of the pocket.[18]
- CAL as the distance from the base of the pocket and the cement–enamel junction.[19]

Gingival Crevicular Fluid Samples Collection

GCF samples were taken from the location with the greatest CAL (3–5 mm or more) and probing depth (≥4 mm) scores. Using a cotton roll, the teeth chosen for sampling were separated, and supragingival plaque was extracted without coming into contact with the marginal gingiva. GCF was obtained by gently stroking the gingival edge with a preadjusted microcapillary pipette at the gingival sulcus entry until a standardized amount of 1 µL was obtained.[20] The GCF samples were promptly placed into Eppendorf tube vials that held 100 µL of phosphate buffer saline, and the samples were frozen at −80°C till the assessment of IL 1β (►**Fig. 2**).

IL 1β Analysis

In accordance with the manufacturer's guidelines, IL-1β levels in the samples were determined using an enzyme-linked immune-sorbent assay (ELISA; Stat Fax 2100 Reader Awareness Technology, Inc., Florida, USA). IL-1β concentration in GCF samples from individuals with periodontitis was determined utilizing a highly sensitive ELISA kit (Koma Biotech, Korea), where the result was measured in picograms per milliliter (pg/mL).

Statistical Analysis

The mean and standard deviation values were calculated for each group in each test. Data were explored for normality using Kolmogorov–Smirnov and Shapiro–Wilk tests; PI and GI data showed a nonparametric (not-normal) distribution (scores), while the rest of the data showed a parametric (normal) distribution. For nonparametric data, Mann–Whitney test

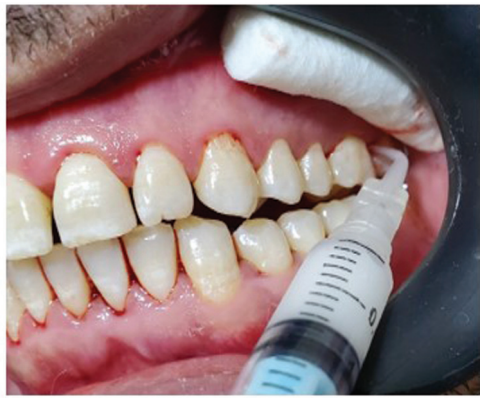

Fig. 1 Intrapocket application of resveratrol gel.

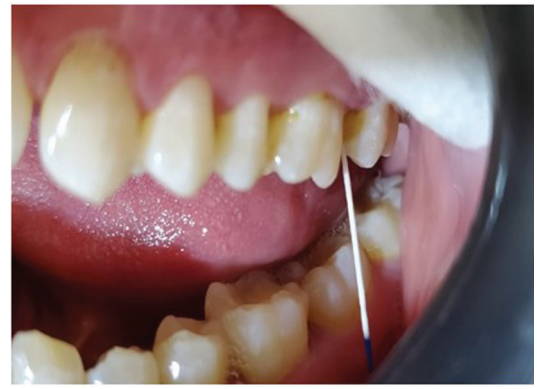

Fig. 2 Gingival crevicular fluid samples collection.

Table 1 Values of PI scores through treatment intervals among the study groups

		PI			
		Baseline	After 3 mo	After 6 mo	*p*-Value
Group I: *N* (20) Patients treated with SRP	Mean ± SD	1.97 ± 0.35	0.93 ± 0.41	0.71 ± 0.32	<0.001 S
Group II: *N* (20) Patients treated with SRP plus adjunctive RES	Mean ± SD	1.93 ± 0.35	0.86 ± 0.29	0.92 ± 0.40	<0.001 S
	p-Value	0.734 NS	0.528 NS	0.149 NS	

Abbreviations: NS, nonsignificant ($p > 0.05$); PI, plaque index; RES, resveratrol; S, significant ($p < 0.05$); SD, standard deviation; SRP, scaling and root planning.

was used to compare between two groups in nonrelated samples, and the Friedman test was used to compare between more than two groups in related samples. The Wilcoxon test was used to compare between two groups in related samples. For parametric data, an independent sample *t*-test was used to compare between two groups in nonrelated samples. A repeated measures ANOVA was used to compare between more than two groups in related samples. IBM SPSS Statistics Version 20 for Windows was utilized for data analysis. To compare between two groups, a paired sample *t*-test was applied. Spearman correlation was utilized to find the correlation between different parameters. A significance level of $p \leq 0.05$ was set.

Results

Characteristic of Plaque Index Scores during Treatment Periods

When comparing PI values, there was a significant reduction in overall mean PI scores in the same patient group through different treatment intervals baseline, 3 months, and 6 months (1.97 ± 0.35, 0.93 ± 0.41, and 0.71 ± 0.32), respectively, in patients treated with SRP and (1.93 ± 0.35, 0.86 ± 0.29, and 0.92 ± 0.40), respectively, in patients treated with SRP plus adjunctive RES ($p < 0.05$); however, in patients treated with SRP plus adjunctive RES, no significant difference was found between 3 and 6 months intervals. When comparing patients treated with SRP with patients treated with SRP plus adjunctive RES, PI scores showed no significant difference at baseline, 3 months, and 6 months treatment intervals ($p = 0.734$, 0.528, and 0.149, respectively; ►**Table 1**).

Characteristic of Gingival Index Scores during Treatment Periods

With regard to GI scores, a significant difference between different treatment intervals was reported in the same patient group allover treatment periods baseline, 3 months, and 6 months: 1.83 ± 0.36, 0.79 ± 0.42, and 0.74 ± 0.29, respectively, in patients treated with SRP; and 1.94 ± 0.33, 0.81 ± 0.34, and 0.72 ± 0.38, respectively, in patients treated with SRP plus adjunctive RES ($p < 0.05$). However, there was no significant difference found between 3 and 6 months intervals in both patient groups. When comparing patients treated with SRP with those treated with SRP plus adjunctive RES, GI scores showed no significant difference at baseline, 3 months, and 6 months treatment intervals ($p = 0.381$, 0.784, and 0.634, respectively; ►**Table 2**).

Characteristic of Probing Pocket Depth during Treatment Periods

With regard to PPD scores, a significant difference was reported in the same patient group between different treatment intervals baseline, 3 months, and 6 months: 3.89 ± 0.68, 2.56 ± 0.51, and 2.33 ± 0.59, respectively, in patients treated with SRP; and 4.06 ± 0.73, 5.00 ± 2.33, and 1.89 ± 0.76, respectively, in patients treated with SRP plus adjunctive RES ($p < 0.05$). However, in patients treated with SRP, no significant difference was found between 3 and 6 months intervals. Additionally, when comparing patients treated with SRP with those treated with SRP plus adjunctive RES, PPD scores showed no significant difference at baseline, 3 months, and 6 months treatment intervals ($p = 0.481$, 0.190, and 0.059, respectively; ►**Table 3**).

Table 2 Values of GI scores through treatment intervals among the study groups

		GI			
		Baseline	After 3 mo	After 6 mo	*p*-Value
Group I: *N* (20) Patients treated with SRP	Mean ± SD	1.83 ± 0.36	0.79 ± 0.42	0.74 ± 0.29	<0.001 S
Group II: *N* (20) Patients treated with SRP plus adjunctive RES	Mean ± SD	1.94 ± 0.33	0.81 ± 0.34	0.72 ± 0.38	<0.001 S
	p-Value	0.381 NS	0.784 NS	0.634 NS	

Abbreviations: GI, gingival index; NS, nonsignificant ($p > 0.05$); RES, resveratrol; S, significant ($p < 0.05$); SD, standard deviation; SRP, scaling and root planning.

Table 3 Values of (PPD) scores through treatment intervals among the study groups

		PPD			
		Baseline	After 3 mo	After 6 mo	*p*-Value
Group I: *N* (20) Patients treated with SRP	Mean ± SD	3.89 ± 0.68	2.56 ± 0.51	2.33 ± 0.59	<0.001 S
Group II: *N* (20) Patients treated with SRP plus adjunctive RES	Mean ± SD	4.06 ± 0.73	5.00 ± 2.33	1.89 ± 0.76	<0.001 S
	p-Value	0.481 NS	0.190 NS	0.059 NS	

Abbreviations: NS, nonsignificant ($p > 0.05$); PPD, probing pocket depth; RES, resveratrol; S, significant ($p < 0.05$); SD, standard deviation; SRP, scaling and root planning.

Characteristic of Clinical Attachment Level during Treatment Periods

Within CALs, a significant difference was reported in the same patient group between different treatment intervals baseline, 3 months, and 6 months: 3.00 ± 0.77, 1.67 ± 0.59, and 1.44 ± 0.62, respectively, in patients treated with SRP; and 3.00 ± 0.69, 1.61 ± 0.70, and 1.28 ± 0.46, respectively, in patients treated with SRP plus adjunctive RES ($p < 0.05$). However, in patients treated with SRP only, no significant difference was found between 3 and 6 months intervals. Moreover, when comparing patients treated with SRP only and those treated with SRP and adjunctive RES, CALs showed no significant difference at baseline, 3 months, and 6 months treatment intervals ($p = 1$, 0.799, and 0.364, respectively; ►**Table 4**).

Variations of Interleukin-1β Levels during Treatment Periods

Regarding IL-1β levels, a significant difference was reported in the same patient group between different treatment intervals baseline, 3 months, and 6 months: 2222.83 ± 352.86, 1999.50 ± 315.75, and 1977.17 ± 240.77, respectively, in patients treated with SRP; and 2148.06 ± 272.24, 1915.94 ± 158.46, and 1832.28 ± 162.62, respectively, in patients treated with SRP plus adjunctive RES ($p < 0.05$), while in patients treated with SRP, no significant difference was found between 3 and 6 months intervals. Moreover, when comparing patients treated with SRP with those treated with SRP and adjunctive RES, IL-1β levels showed no significant difference at baseline and 3 months treatment intervals ($p = 0.481$ and 0.323, respectively), while there was a significant difference at 6 months interval ($p = 0.042$; ►**Table 5**).

Correlation between Interleukin-1β and Different Clinical Parameters

With regard to correlation of the inflammatory marker IL-1β with different clinical parameters, it showed positive correlation with all parameters. IL-1β showed positive correlation

Table 4 Values of CAL in mm through treatment intervals among the study groups

		CAL			
		Baseline	After 3 mo	After 6 mo	*p*-Value
Group I: *N* (20) Patients treated with SRP	Mean ± SD	3.00 ± 0.77	1.67 ± 0.59	1.44 ± 0.62	<0.001 S
Group II: *N* (20) Patients treated with SRP plus adjunctive RES	Mean ± SD	3.00 ± 0.69	1.61 ± 0.70	1.28 ± 0.46	<0.001 S
	p-Value	1 NS	0.799 NS	0.364 NS	

Abbreviations: CAL, clinical attachment level; NS, nonsignificant ($p > 0.05$); RES, resveratrol; S, significant ($p < 0.05$); SD, standard deviation; SRP, scaling and root planning.

Table 5 Levels of IL-1β in pg/mm through treatment intervals among the study groups

		PI			
		Baseline	After 3 mo	After 6 mo	*p*-Value
Group I: *N* (20) Patients treated with SRP	Mean ± SD	2222.83 ± 352.86	1999.50 ± 315.75	1977.17 ± 240.77	<0.001 S
Group II: *N* (20) Patients treated with SRP plus adjunctive RES	Mean ± SD	2148.06 ± 272.24	1915.94 ± 158.46	1832.28 ± 162.62	<0.001 S
	p-Value	0.481 NS	0.323 NS	0.042 S	–

Abbreviations: IL-1β, interleukin-1β; NS, nonsignificant ($p > 0.05$); PI, plaque index; RES, resveratrol; S, significant ($p < 0.05$); SD, standard deviation; SRP, scaling and root planning.

Table 6 Correlation between IL-1β and different clinical parameters

		PI	GI	PDD	CAL	IL-1β
IL-1β	Spearman correlation	0.337[a]	0.317 [a]	0.377[a]	0.256[a]	1.000
	p-Value	0.000 S	0.001 S	0.000 S	0.008 S	–

Abbreviations: CAL, clinical attachment level; GI, gingival index; IL-1β, interleukin-1β PPD, probing pocket depth; PI, plaque index; S, significant ($p < 0.05$).
[a]There was a correlation.

with PI, GI, PDD, and CAL, with *p*-values of 0.000, 0.001, 0.000, and 0.008, respectively (►**Table 6**).

Discussion

Periodontitis is a chronic multifactorial inflammatory disease that causes a gradual deterioration of the supporting periodontal tissues.[21] Periodontal treatment is primarily intended to halt the progression of inflammatory disease. Subgingival biofilm is mechanically removed during treatment, and a local microbiome and environment conducive to periodontal health are established.[22]

RES is a polyphenol that is synthesized by plants in response to microbial, fungal, and chemical threats.[23] Moreover, it has neuroprotective, anticarcinogenic, antibacterial, and anti-inflammatory properties.[24]

RES inhibits NF-kB-dependent cell adhesion molecules in *Porphyromonas gingivalis* LPS-induced monocyte adherence to the endothelium, indicating that it may have a therapeutic impact on periodontal pathogen-induced vascular inflammation.[25] Additionally, its immunomodulatory activity leads to the downregulation of inducible NO synthase, as seen by the decrease in systemic levels of certain proinflammatory cytokines.[26]

B cells, macrophages, monocytes, and natural killers all release IL-1β, a pleiotropic cytokine with several functions.[27] It has a crucial role in the pathogenesis of periodontitis and is a crucial modulator of the inflammatory response, cell proliferation, differentiation, and apoptosis.[28] IL-1β induces the generation of tissue-degrading proteinases, making it a highly effective inducer of periodontal tissue resorption.[29] In periodontitis, it is involved in inflammation, immunological modulation, and bone resorption.[30] The average level of IL-1β obtained from inflamed pockets was three times more than that from noninflamed pockets. However, the level of IL-1β dropped following the initial treatment.[31]

In this study, smokers, pregnant, medically compromised patients, and patients under an antibiotic, immunosuppressive, and/or anti-inflammatory drug regimen at or prior to the study that could affect the results of this research were excluded. This is in agreement with the criteria established by the Cornell Medical Index and its modification.[32]

The current study was designed using the whole mouth technique to mitigate a potential drawback associated with the split-mouth design: carry-across effects, which arise when the treatment administered in one area of the mouth can influence the treatment response in other areas, potentially introducing bias to the results.[33]

The time period for clinical evaluation was 6 months, since this time was considered enough for clinical and biochemical evaluation of cases included in this study. To prevent unwanted effects on healing tissues, which are delicate and susceptible to harm during the probing procedure, no measurements were collected from the baseline until 3 months after treatment. This was done as healing in the sulcus starts at the lower portion of the pocket.[19]

GCF analysis has been used in this research to assess the activity of periodontitis and to clarify the outcome of periodontal treatment; GCF is suitable for the detection of biochemical markers as an indicator of the activity of periodontal disease.[34] In addition, there is a positive relationship between the level of inflammatory mediators in GCF and clinical periodontal parameters.[35]

Results of this study showed that, with regard to oral hygiene indices, there was a significant reduction in PI and GI scores from baseline to 6 months in both groups as compared with their baseline ($p < 0.05$). However, there was no significant difference between patients treated with SRP with those treated with SRP plus adjunctive RES at different periods of treatment ($p < 0.05$), these findings may be explained by that, oral hygiene was maintained and reinforced in all patients during the observation duration of the research and also may be attributed to the design of the study itself, which eliminates intersubject variance.

With regard to change in PPD and CAL, a statistically significant difference is reported between different intervals in comparison to baseline in both groups ($p < 0.05$). In contrast, in patients treated with SRP plus RES, a significant difference is observed between 3 and 6 months in contrast to patients treated with SRP, and this is in agreement with another study, which used RES in stage III periodontitis with smoker patients to explore its antioxidant effect, which concluded a significant variation in PPD and CAL between 3 and 6 months in patients treated with RES.[36] This may be attributed to RES antioxidant, anti-inflammatory, and ability to stimulate osteoblastic cells.[36]

There is another recent study[5] that used oral RES for 8 weeks in patients with periodontitis in three different concentrations and found that there was significant reduction at the end of study in both CAL and PPD when comparing test group to control group and also found that there is more reduction in high dose group than medium and low doses but this decrease is not statistically significant, this difference with current study may be attributed to drug maintenance throughout 8 weeks which maintains concentration of drug.

Additionally, when both groups were compared in regard to PPD and CAL, no significant difference was reported at different intervals of study.

In correlation of clinical parameters to inflammatory cytokine IL-1β, there was significant association found showing that improvement of the patient's clinical state is accompanied by a corresponding drop in inflammatory mediator.

With regard to IL-1β level, a statistically significant difference was found at various intervals in comparison to baseline in both groups; however, insignificant variation was found between 3 and 6 months in patients treated with SRP. In contrast to patients treated with SRP plus RES, a significant variation was found between 3 and 6 months($p < 0.05$), indicating that addition of RES may give better outcome due to its anti-inflammatory properties.

When comparing two groups at baseline and 3 months, no significant variation was found between the two groups while there was a significant variation between them at 6 months with more reduction in IL-1β level in group II giving superiority to the addition of RES in therapy. This is in agreement with a study[36] which found improvement in biochemical markers when comparing the test to the control group, and this is explained by the anti-inflammatory and antioxidant effect of RES.

Moreover, the result of another study[5] found that there was a systemic and local significant reduction in IL-1β and other proinflammatory markers in the test group in comparison to the control group and also when comparing high doses to low doses, and this finding is in agreement with the current study which aims to explore the anti-inflammatory effect of RES in periodontitis patients.

Also, another in vitro study[37] which used human PDL stimulated with *P. gingivalis* and treated with RES in different concentrations showed that IL-1β was significantly reduced in the test group in comparison to the control group, and this reduction is directly related to the concentration of RES, and this finding is in agreement with the current study and with the anti-inflammatory effect of RES.

Although previous findings do not coincide with other in vivo study,[38] which find no significant reduction in IL-1β between different groups, it has been documented that treatment with RES is accompanied by higher inhibition of cytokines.

Another in vivo study[39] used systemic RES alone and in combination with other polyphenol material in the treatment of periodontitis, it showed no significant reduction in IL-1β between groups when using RES alone while there was a significant reduction when used in combination with other material and difference between these studies and current study may be due to topical use of RES in the current study which provides high concentration of RES consequently more potent and more anti-inflammatory effect.

Conclusion

Considering the limitations of this study, our findings support RES as supplementary to improve periodontitis therapy and RES may play a role in improvement of periodontitis through anti-inflammatory effects. Further long-term studies are recommended to evaluate the therapeutic effect of RES and better in comparison to other medicines through a large populations patient with periodontitis.

Conflicts of Interest

None declared.

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