

ORIGINAL RESEARCH

Comparative Evaluation of Locally Delivered Lycopene Gel and Coenzyme Q10 Gel as an Adjunct in the Treatment of Chronic Periodontitis: A Clinico-Biochemical Study

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ABSTRACT

In this study, lycopene, an antioxidant, has been compared to coenzyme Q-10, another potent antioxidant, to evaluate their efficacy on gingival crevicular fluid (GCF) tumor necrosis factor- α (TNF- α) levels, correlating with the clinical parameters in chronic periodontitis patients and comparing them with the control group. 30 subjects were selected on basis of inclusion criteria and were categorized into three treatment groups. After subject selection, 15 patients were randomly (by coin toss) assigned to the first group that is the control group, and split-mouth study was done on the remaining 15 patients in which the right side and left side were assigned as a second group and third group, respectively. The patients selected were subjected to assessment of modified Sulcus Bleeding Index (SBI), probing depth (PD), and relative attachment level. TNF- α level was measured by collecting GCF samples from the selected sites (Jaganath *et al.* 2011). The clinical parameters were assessed at baseline, 1 month, and 3 months postoperatively, whereas TNF- α was assessed at baseline and 1 month postoperatively. This study showed that both lycopene and coenzyme Q10 are effective in reducing the clinical parameters (mSBI and PD) and gain in relative attachment level. The anti-inflammatory effect, i.e. percentage change in GCF TNF- α level is more significant in Group III (coenzyme Q10) than Group II (lycopene). Thus, coenzyme Q10 plays a better role in improving gingival health by reducing the level of pro-inflammatory markers, i.e., TNF- α .

Keywords: Chronic periodontitis, Coenzyme Q10 gel, Lycopene gel.

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INTRODUCTION

The concept of local drug delivery was championed by Dr. Max Goodson in the year 1979. Local drug delivery allows the use of concentrations of approximately 100 times higher than does systemic administration.

A locally delivered product must remain in the pocket long enough to be effective. The goal of locally delivered products should be to eliminate the pathogenic microorganisms or alter the inflammatory response and thereby minimize tissue destruction.

Goodson (1985) suggested three important criteria for successful local drug delivery that includes:

1. Device must deliver drug to the base of the pocket.
2. It must deliver drug at microbiologically efficacious concentration.
3. It must sustain the concentration of the drug in the pocket for sufficient length of time and in sufficient concentration to be clinically effective.^[1]

Lycopene, a non-provitamin A carotenoid, is responsible for the red to pink colors seen in tomatoes, pink grapefruit, and other foods of fruit and vegetable origin. Processed tomato products are the primary source of dietary lycopene.^[2]

Coenzyme Q10 (CoQ10) is a compound found naturally in the energy-producing center of the cell known as the mitochondria. Physiologically, CoQ10 plays four major roles. It has an essential role in mitochondrial energy (ATP) production through redox activity in the respiratory chain, transporting electrons between enzymes. Second, it plays a role in extramitochondrial redox activity in the cell membrane and endomembranes. CoQ10 also functions as an antioxidant, inhibiting lipid peroxidation and scavenging free radicals. Finally, it plays an important role in membrane stabilization and fluidity.

Patients with periodontal disease have low concentrations of CoQ10 in gingival tissue and blood. This has led some clinical investigators and dentists to recommend CoQ10 supplementation, particularly for diabetic patients and others at risk for periodontal disease.

Bessler (2008; 20010),^[3,4] Hung (2008),^[5] and Jin (2013)^[6] in their respective studies concluded that lycopene and CoQ10 exert a effect on cytokine production by its capacity to modulate human immune function and hence decrease tumor necrosis factor- α (TNF- α).

Therefore, the present study intends to compare lycopene to coenzyme Q-10, both of which are anti-oxidant, and to evaluate their efficacy on gingival crevicular fluid (GCF) TNF- α levels by correlating them with the clinical parameters in chronic periodontitis patients and comparing them with the control group.

MATERIALS AND METHODS

1–5 μ L calibrated volumetric microcapillary pipettes (Sigma-Aldrich Chemicals Company Ltd., USA), Eppendorf tubes, 2% lycopene gel, 2% coenzyme Q-10 gel, and blunt cannula needle enzyme-linked immunosorbent assay were used for the analysis of TNF- α (Immunoconcept India Pvt., Ltd.).

Source of Data

Patients within the age range of 25–55 years of both the sexes were selected from the outpatient Department of Periodontology, after the approval of the Ethical Committee of the D. J. College of Dental Sciences and Research, Modinagar, Uttar Pradesh. Each patient was given a detailed verbal and written description of the study.

Inclusion Criteria

The following criteria were included in the study:

1. Systemically healthy patients with chronic periodontitis having a pocket depth of 4–8 mm.
2. No history of antibiotic or periodontal therapy in the preceding 6 months.
3. Age group of 25–55 years.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patients with aggressive periodontitis, smokers, alcoholics, diabetes, hypertension, immunocompromised patients, and pregnant or lactating mothers.
2. Patients with dental infections such as chronic peri-apical lesions, aphthous stomatitis, and oral lichen planus.
3. Patients with known or suspected allergy to the lycopene or coenzyme Q-10.
4. Patients on systemic lycopene and coenzyme Q-10 therapy or antibiotic therapy.

Study Design

30 subjects were selected on the basis of inclusion criteria were categorized into three treatment groups. After subject selection, 15 patients were randomly (by coin toss) assigned to first group that is the control group, and split-mouth study was done on the remaining 15 patients in which the right side and left side were assigned as second group and third group, respectively.

Group I ($n = 15$): Patients treated by SRP alone.

Group II ($n = 15$): Split mouth (right side).

Patients treated by SRP with subgingival 2% lycopene gel.

Group III ($n = 15$): Split mouth (left side).

Patients treated by SRP with subgingival 2% coenzyme Q-10.

Clinical Measurements

At each patient's initial appointment, baseline data were obtained on modified Sulcus Bleeding Index (mSBI) by the method of Mombelli A on four posterior teeth in each quadrant (1st premolar, 2nd premolar, 1st molar, and 2nd molar). Probing depth (PD) and relative attachment level (custom-made occlusal stent) were measured with a UNC-15 periodontal probe for the same teeth. GCF samples were taken at 16 sites for each patient.

These sites were the mesiobuccal surfaces of the above stated 4 posterior teeth in each upper quadrant and at the mesiolingual surfaces of the same in each lower quadrant. SRP performed until the root surface is considered smooth and clean by the operator. Scaling and root planning (SRP) were performed in both the groups. No antibiotics or anti-plaque and anti-inflammatory agents were prescribed after treatment. 1–3 months later, these measurements (mSBI, PD, and RAL) and GCF sampling were repeated [Figure 1].

Collection of GCF

Each GCF sample was collected for 15 s by calibrated volumetric microcapillary pipettes which inserted in the gingival sulcus immediately after the area has been isolated with cotton rolls, dried, and supragingival plaque has been removed with a sterile Gracey curette. The calibrated volumetric microcapillary pipettes were placed in a polypropylene tube and immediately transferred to plastic vial and then stored at -70°C till the time of assay.

Microcapillary pipettes contaminated with blood and saliva were excluded from the sampled group. GCF sample was collected again after 1 month [Figure 2].

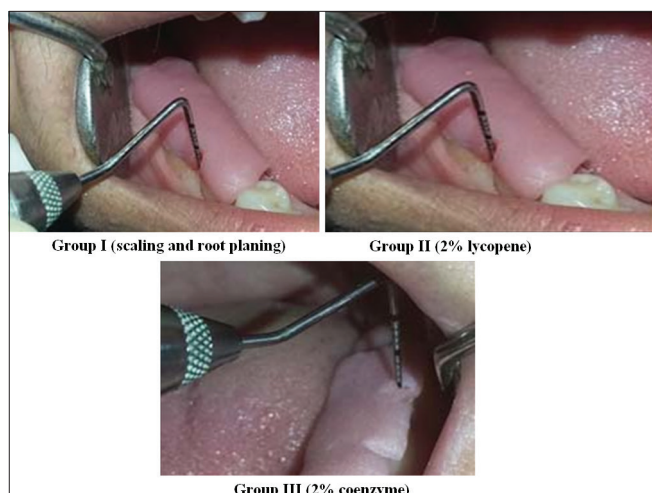


Figure 1: Pre-operative clinical measurements



Figure 2

GCF Analysis

Biochemical analysis of GCF samples was done to estimate the level of TNF- α using ELISA kit (Boster Immunoleader Human TNF- α ELISA KIT).

Formulation of Lycopene Gel

Lycopene gel was prepared in the Department of Pharmacology, D. J. College of Dental Sciences and Research, Modinagar. 105 mg of methylcellulose was added into 5 mL of distilled water and stirring was done at 50–60°C to make a gel form (Solution A).

A weighed amount of lycopene was added to the above solution and dissolved completely to obtain a homogeneous phase of polymer, solvent, and drug. Thus, the lycopene *in situ* gel was prepared with a concentration of 2%.

Local Drug Delivery

For standardization, lycopene gel 0.1 mL prepared (2%) was injected into the periodontal pockets using a syringe with a blunt cannula in Group I and 0.1 mL

of coenzyme Q-10 gel (2%) was injected into the periodontal pockets using a syringe with a blunt cannula in Group II. No periodontal dressing applied after delivery of the drug because the prepared formulation decreases in viscosity, which causes swelling and occlusion of the periodontal pocket. After placement of the gel *in situ*, patients instructed to refrain from chewing hard or sticky foods, brushing near the treated areas, or using any interdental aids for 1 week [Figure 3].

1 and 3 months later, all clinical measurements were repeated for both the groups and GCF samples were evaluated again after 1 month. A single clinician provided treatment to both groups, and all pre- and post-treatment clinical parameters were recorded by the same examiner.

Considering aim and objectives, this study was designed in three treatment groups: Group I–III.

- Group I patients were treated with SRP alone.
- Group II patients were treated with SRP along with subgingival application of 2% lycopene gel.
- Group III patients were treated with SRP along with subgingival application of 2% coenzyme Q-10 gel.

Control of plaque and gingivitis is important in clinical studies because both vary in their association with periodontitis and both affect measured response to therapy. Since PD and loss of relative attachment are pathogenomic for periodontitis, pocket probing is a crucial and mandatory procedure in diagnosing periodontitis and evaluating the success of periodontal therapy.

The patients selected were subjected to the assessment of mSBI, PD, and relative attachment level. UNC-15 probe (Guentsch *et al.* 2008)^[7] and occlusal stent were used as a reference point (Clark *et al.* 1987).^[8]

TNF- α level was measured by collecting GCF samples from the selected sites (Jaganath *et al.* 2011).^[9] The clinical parameters were assessed at baseline, 1 month, and 3 months postoperatively, whereas TNF- α was assessed at baseline and 1 month postoperatively.

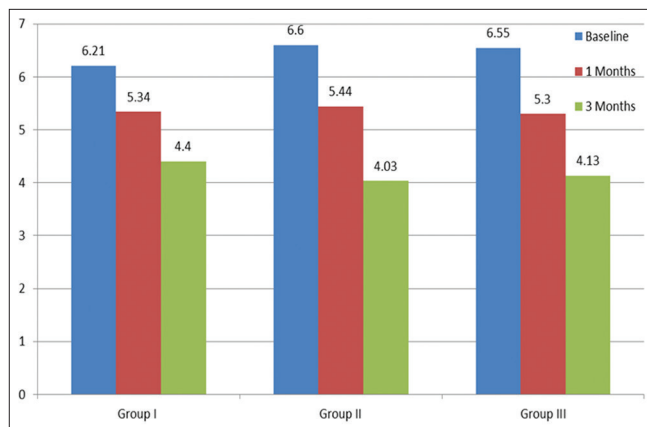
In this present study, GCF TNF- α level estimation has been performed since it is a potential prognostic biomarker of periodontal disease activity.

Heralgi *et al.*, in a clinical study, concluded that TNF- α plays a key role in the progression of periodontal disease and also provides site-specific information on changes in TNF- α levels serving as a strong clinical marker of disease activity.^[10]

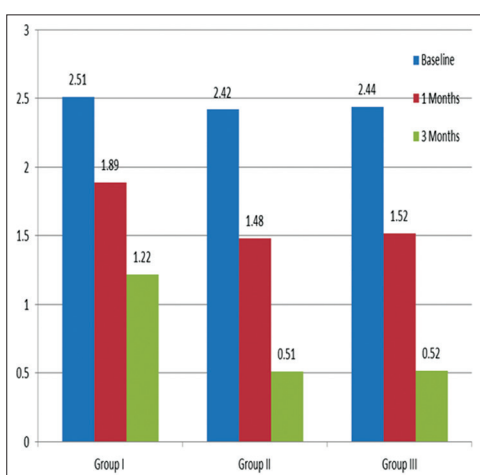
A similar study by Gokul suggested a positive association between periodontal disease and increased levels of TNF- α in GCF and serum and a possibility of using the estimation of TNF- α in GCF as a “marker” of periodontal disease.^[11]



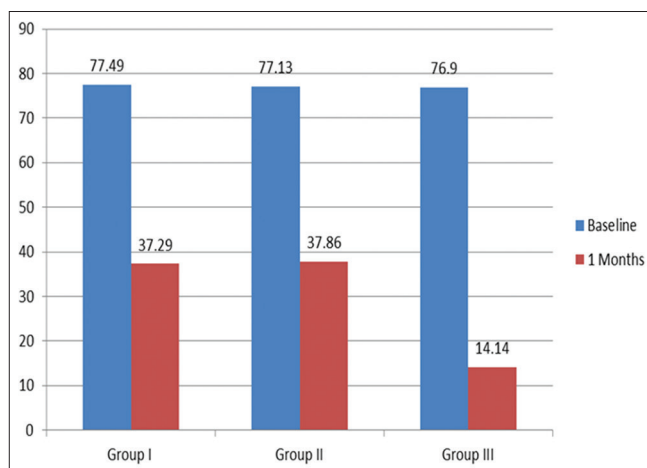
Figure 3



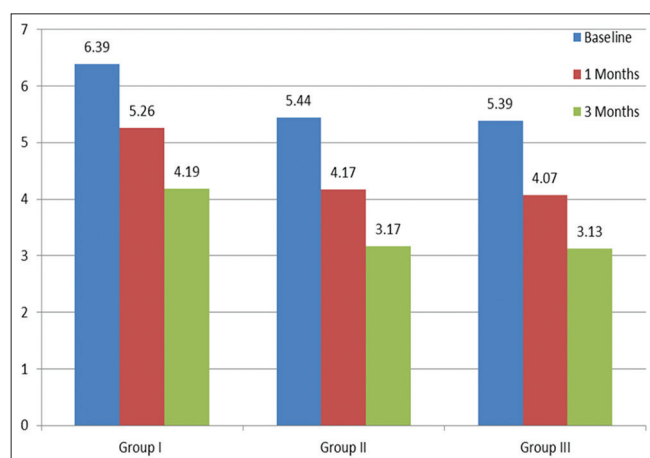
Graph 3: Intragroup comparison of cal scores b/w three interval for Group I-III



Graph 1: Intragroup comparison of modified Sulcus Bleeding Index between three intervals for Groups I-III



Graph 4: Intragroup comparison of tumor necrosis factor levels between the different intervals - baseline and 1 month.



Graph 2: Intragroup comparison of probing depth scores between three intervals for Groups I-III

CLINICAL OBSERVATIONS

Possible side effects of therapy including slight discomfort and gingival redness were evaluated. No treatment-related adverse effects were observed in any patient.

Intragroup comparison of groups between the different intervals Group I.

Intragroup comparison of Group I (scaling and root planing) between the different intervals shows that there is a significant reduction in mean scores of mSBI, PD, and gaining CAL at baseline, 1 month, and 3 months. Thus, it shows that scaling and root planing are efficient in reducing gingival bleeding, PD, and gaining CAL.

- Group II
Intragroup comparison of Group II (lycopene) between the different intervals shows that there is a significant reduction in mean scores of mSBI, PD, and gaining CAL at baseline, 1 month, and 3 months. Thus, it shows that lycopene is efficient in reducing gingival bleeding, PD, and gaining CAL.
- Group III
Intragroup comparison of Group III (coenzyme Q10) between the different intervals shows that there is a significant reduction in mean scores of mSBI, PD, and gaining CAL at baseline, 1 month, and 3 months. Thus, it shows that coenzyme Q10 is efficient in reducing gingival bleeding, PD, and gaining CAL.

Intragroup Comparison of Clinical Parameters between the Different Intervals

There is a significant reduction in the mean scores for mSBI in all the groups at all intervals, but it is more significant in Group II (lycopene) and Group III (coenzyme Q10). Thus, it shows that lycopene and coenzyme Q10 are more efficient in reducing gingival bleeding.

There is a significant reduction in the mean scores for PDI in all the groups at all intervals, but it is more significant in Group II (lycopene) and Group III (coenzyme Q10). Thus, it shows that lycopene and coenzyme Q10 are more efficient in reducing PD.

There is a significant reduction in the mean scores for CAL in all the groups at all intervals, but it is more significant in Group II (lycopene) and Group III (coenzyme Q10). Thus, it shows that lycopene and coenzyme Q10 are more efficient in gaining CAL.

Intergroup Analysis between Lycopene and Coenzyme Q10 Group

There is statistically non-significant differences in both lycopene and coenzyme Q10 group. Thus, both lycopene and coenzyme Q10 are efficient in decreasing gingival bleeding.

There are statistically non-significant differences in both lycopene and coenzyme Q10 group. Thus, both lycopene and coenzyme Q10 are efficient in decreasing PD.

There is statistically non-significant differences in both lycopene and coenzyme Q10 group. Thus, both lycopene and coenzyme Q10 are efficient in gaining CAL.

Biochemical Observations (GCF TNF-α Level)

Intergroup comparison of percentage change in GCF TNF-α

Table 1: Intragroup comparison of Gingival Bleeding Index scores between the different intervals - baseline, 1 month, and 3 months

	Baseline	1 month	3 months	P value	Significance
Group I	2.51±0.53	1.89±0.37	1.22±0.30	0.001	Significant
Group II	2.42±0.08	1.48±0.06	0.51±0.07	0.001	Significant
Group III	2.44±0.10	1.52±0.09	0.52±0.07	0.001	Significant

Table 2: Intragroup comparison of PD scores between the different intervals - baseline, 1 month, and 3 months

	Baseline	1 month	3 months	P value	Significance
Group I	6.39±0.48	5.26±0.31	4.19±0.51	0.001	Significant
Group II	5.44±0.38	4.17±0.26	3.17±0.20	0.001	Significant
Group III	5.39±0.31	4.07±0.30	3.13±20	0.001	Significant

PD: Probing depth

Both the groups, lycopene and coenzyme Q10, show a significant percentage change in the scores of GCF TNF-α, but change is more evident in Group III (coenzyme Q10). Thus, it shows that coenzyme Q10 is more efficient in reducing GCF TNF-α level compared to lycopene.

Intragroup comparison of GCF TNF-α for Group I–III

There is a significant reduction in the mean scores for GCF TNF-α in all the groups at both intervals, but the change is most evident in Group III (coenzyme Q10). Thus, it shows that coenzyme Q10 is more efficient in reducing GCF TNF-α compared to lycopene and scaling and root planing.

DISCUSSION

Recent development of science and technology has revolutionized the basic outlook and approach to the problems of periodontal disease. The most widely used approach has been SRP. Debridement of the root surface by SRP came into relatively common use in the first half of the past century and has become the central feature held in common by all currently used forms of periodontal therapy.^[8] However, complex anatomy of the pocket and roots and the contours of the lesion are significant limiting factors, as complete mechanical access may not always be possible. Hence, mechanical conventional periodontal treatment alone may not be effective, and sufficient reduction of the bacterial load may not be provided. Moreover, the success of mechanical periodontal treatment is closely related to the patient's performance of daily plaque control.

Hence, antimicrobial agents are of great interest and may be valuable as adjuncts to mechanical therapy in treating periodontal pockets. Systemic administration of antimicrobial drugs involves a relatively high dose with repeated intake over a prolonged period of time to achieve the required inhibitory concentrations in the sulcular fluid. This increases the chances of development of

Table 3: Intragroup comparison of CAL index scores between the different intervals - baseline, 1 month, and 3 months

	Baseline	1 month	3 months	P value	Significance
Group I	6.21±0.43	5.34±0.54	4.40±0.74	0.001	Significant
Group II	6.60±0.30	5.44±0.45	4.03±0.62	0.001	Significant
Group III	6.55±0.26	5.30±0.56	4.13±0.45	0.001	Significant

Table 4: Intragroup comparison of GCF TNF-α levels between the different intervals - baseline and 1 month

	Baseline	1 month	P value	Significance
Group I	77.49±6.21	37.29±8.60	0.001	Significant
Group II	77.13±6.42	37.86±7.13	0.001	Significant
Group III	76.90±6.73	14.14±2.78	0.001	Significant

GCF: Gingival crevicular fluid, TNF: Tumor necrosis factor-α

resistance, alteration of commensal flora, and increased potential for adverse effects such as nausea, vomiting, hypersensitivity, gastrointestinal intolerance, and the development of bacterial resistance.^[9] Local administration, therefore, provides a useful answer to these problems. Local delivery systems offer the advantages of high concentrations at the target sites with reduced systemic dosing, fewer applications, lesser side effects, and high potential acceptability. The local delivery system maintains effective intrapocket levels of antibacterial agents for extended periods of time so that they can alter subgingival flora and influence the healing of attachment apparatus.

In this study, lycopene, an antioxidant, has been compared to coenzyme Q-10, another potent antioxidant, to evaluate their efficacy on GCF TNF- α levels, correlating with the clinical parameters in chronic periodontitis patients and comparing them with the control group.

Lycopene

Lycopene, a member of carotenoid family, is a lipid-soluble antioxidant synthesized by many plants and microorganisms but not by animals and humans where it serves as an accessory light-gathering pigment and protects them against the toxic effects of oxygen and light. It is a red pigment without provitamin A activity that imparts color to many fruits and vegetables. The ideal intake of lycopene is currently indefinite; however, one study suggested that at least 5–10 g of fat in a meal is required for lycopene absorption and 6 mg/day of lycopene is beneficial for prostate cancer prevention.^[10]

Role in Periodontal Health

The study that used systemically administered lycopene was developed by Chandra *et al.*,^[11] and they analyzed its effect in the treatment of gingivitis. They stated that sites treated with lycopene and oral prophylaxis significantly reduced more gingivitis when compared with both control groups. In addition, gingivitis patients who were treated only with lycopene showed a greater improvement compared with the group that was treated with the placebo only.

Lycopene was also used locally in two studies complementarily for SRP.^[11,12] One of these studies showed that lycopene-treated sites presented significantly higher levels of PD reduction and more clinical attachment gain when compared to sites treated with placebo gel, despite smoking habits. The study also showed that periodontal treatment was capable of reducing the serum levels of 8-hydroxydeoxy-guanosine, a biomarker of oxidative damage.^[10] In addition, the lycopene-treated sites in nonsmokers, when compared to smokers, benefited

more from this reduction, achieving levels quite similar to those of periodontal healthy individuals.

Coenzyme Q10

It also known as ubiquinone was discovered by Crane *et al.* in 1957 in beef heart mitochondria. It was first isolated from the mitochondria of bovine hearts in 1957 at the University of Wisconsin. Identification of the chemical structure and synthesis was completed by 1958.

Physiologically, CoQ10 plays four major roles. It has an essential role in mitochondrial energy (ATP) production through redox activity in the respiratory chain, transporting electrons between enzymes. Second, it plays a role in extramitochondrial redox activity in the cell membrane and endomembranes. CoQ10 also functions as an antioxidant, inhibiting lipid peroxidation and scavenging free radicals. Finally, it plays an important role in membrane stabilization and fluidity.^[13]

CoQ10 and Periodontal Diseases

Periodontal disease (gum disease) affects 60% of young adults and 90% of individuals over the age of 65. Healing and repair of periodontal tissue require efficient energy production. The metabolic functions depend on an adequate supply of CoQ10. CoQ10 deficiency has been reported in gingival tissue of patients with periodontal disease. Gingival biopsies revealed subnormal tissue level of CoQ10 in 60–96% of patients with periodontal disease and low level of CoQ10 in leukocytes in 86% of cases. These finding indicated that periodontal disease is frequently associated with CoQ10 deficiency.^[14]

Patients with periodontal disease have low concentrations of CoQ10 in gingival tissue and blood. This fact has led some clinical investigators and dentists to recommend CoQ10 supplementation, particularly for diabetic patients and others at risk for periodontal disease.^[14] A case report of one patient with severe periodontal disease who had a dramatic improvement with CoQ10 therapy prompted several open-label trials.^[13] In one case series, eight patients with periodontal disease were treated with CoQ10 (50 mg daily); symptoms were significantly reduced over 21 days of treatment. In an open-label study of ten adult patients with periodontal disease, topical therapy with CoQ10 was associated with significant improvement in disease. In an additional open trial, administration of CoQ10 produced extraordinary post-surgical healing (2–3 times faster than normal) in seven patients in advanced periodontal disease.^[15]

Many clinical trials with oral administration of CoQ10 to patients with periodontal disease have been conducted. The results have shown that oral administration of CoQ10 increases the concentration of CoQ10

in the diseased gingiva and effectively suppresses advanced periodontal inflammation and periodontal microorganisms.

Effect of Test Drugs on TNF- α

Bessler, 2008 examined the *in vitro* effect of lycopene on cytokine production by peripheral blood mononuclear cells (PBMC) from 15 healthy subjects. First, 2 × 10 PBMC suspended in 1 mL of conditioned medium was incubated over 24 and 48 h without or with the following concentrations of lycopene: 0.25, 0.5, 1.0, 2.0, and 4.0 μ M. The production of the subsequent cytokines was evaluated: IL-1 β , IL-1 α , IL-2, IL-6, and IL-10, as well as TNF- α and IFN γ . Lycopene induced a dose-dependent increase in IL1 β and TNF- α production and a decrease in IL-2, IL-10, and IFN γ secretion, whereas that of IL-6 and IL-1 α was not affected.³

Bessler, 2010 examined the *in vitro* effect of CoQ10 on cytokine production. TNF secretion was significantly decreased and he concluded that CoQ10 exerts a certain effect on cytokine production by PBMC related to its capacity to modulate human immune function.^[4]

This study showed that:

- Both lycopene and coenzyme Q10 are effective in reducing the clinical parameters (mSBI and PD) and gain in relative attachment level.
- The anti-inflammatory effect, i.e. percentage change in GCF TNF- α level is more significant in Group III (coenzyme Q10) than Group II (lycopene). Thus, coenzyme Q10 plays a better role in improving gingival health by reducing the level of pro-inflammatory markers, i.e. TNF- α .

Results were similar to the studies of Pitale^[16] and Hanioka *et al.*^[17-26] where the application resulted in reducing the clinical parameters (mSBI and PD) and gain in relative attachment level.

Results were contrary to studies of Hans *et al.*^[23] and Sharma *et al.*^[27] where the result was insignificant.

CONCLUSION

With the results of the present study, following conclusions were drawn:

- Both lycopene and coenzyme Q10 are effective in reducing the clinical parameters (mSBI, PD) and gain in CAL.
- The anti-inflammatory effect, i.e. percentage change in GCF TNF- α level is more significant in Group III (coenzyme Q10) than Group II (lycopene). Thus, coenzyme Q10 plays a better role in improving gingival health by reducing the level of pro-inflammatory markers, i.e. TNF- α .

The limitation of this study could be small sample size and observation period.

Hence, more rigorous work needs to be done to confirm the usefulness of the lycopene and coenzyme Q10 as a locally delivered drug which would greatly facilitate the treatment of periodontal diseases.

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