Original Article

Comparative clinical evaluation of a local drug delivery of cranberry and garcinia fruit gel with tetracycline fibers for amelioration of periodontitis: A split mouth study

[1]Department of Pharmacology and Toxicology, Principal K. M. Kundnani College of Pharmacy, [2]Department of Periodontitis, Government Dental College and Hospital, Mumbai, Maharashtra, India

Vandana Panda,[1] Pragya Patidar,[1] Rajesh Gaikwad,[2] Shrutika Borade,[2] Lynette Fernandes[2]

This work belongs to (1) Department of Pharmacology, Principal K. M. Kundnani College of Pharmacy, (2) Department of Periodontitis, Government Dental College and Hospital, Mumbai, Maharashtra, India

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Address for correspondence:
Dr. Vandana Panda, Department of Pharmacology and Toxicology, Principal K. M. Kundnani College of Pharmacy, Jote Joy Building, Rambhau Salgaonkar Marg., Cuffe Parade, Colaba, Mumbai - 400 005, Maharashtra, India.
E-mail: vs.panda@kmkcp.edu.in

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Abstract:

Background: The present study formulates and evaluates a polyberry gel comprising extracts of cranberry (*Vaccinium macrocarpon*) and brindle berry (*Garcinia cambogia*) in patients suffering from chronic periodontitis. **Materials and Methods:** The polyberry gel was evaluated for various physicochemical parameters, *in vitro* permeability and stability, and the active phytoconstituents were quantified by High-performance thin layer chromatography (HPTLC). Total phenolic content, total antioxidants, and ascorbic acid were estimated in the two extracts by *in vitro* assays. Patients suffering from chronic periodontitis with probing pocket depth (PPD) up to 5 mm were divided into 3 groups of 21 patients each and treated with scaling and root planing (SRP) or SRP followed by subgingival placement of polyberry gel or tetracycline fibers (standard). Plaque Index (PI), Gingival Index (GI), PPD, Clinical Attachment Level (CAL), and the salivary aspartate aminotransferase (AST) and C-reactive protein (CRP) levels were recorded at baseline and after 1 month. **Results:** A significant ($P < 0.01$) reduction in the periodontic disease parameters was observed in the standard and gel-treated groups between their baseline and 1-month time-interval readings. The polyberry gel treatment significantly ($P < 0.05$ for AST and $P < 0.01$ for the rest) attenuated the periodontitis-elevated PI, GI PPD, CAL, AST and CRP levels when compared with SRP at the end of the study and was comparable with tetracycline. **Conclusion:** The amelioration of periodontitis and gingival inflammation may be attributed to the potent antioxidant activity of the polyphenolic phytoconstituents of the gel. The polyberry gel may thus be used as a safe adjunct to SRP/tetracycline in chronic periodontitis.

Key words:

Cranberry, *Garcinia cambogia*, mucoadhesive gel, periodontitis, tetracycline fiber

INTRODUCTION

Diseases of the oral cavity, especially of the gums, teeth, and the bone which holds the teeth together are associated with a high risk of health complications such as stroke, diabetes, and cardiovascular disease. Periodontitis is a chronic inflammatory disease of the periodontum (supporting structure of the tooth including the cementum, periodontal ligament, alveolar bone, and gums) caused by the oral microbiota that destroys the periodontium to cause a possible tooth loss as well other health issues. The key factors responsible for triggering inflammation in periodontitis are derived either from subgingival microbiota or from the immune-inflammatory response of the host.[1] Periodontal pathogens release noxious substances such as proteases, ammonia, or hydrogen sulfide which mount inflammatory attacks on structural proteins like collagen, leading to tissue destruction. Lipopolysaccharides and fimbriae present in the oral microbiota (mostly gram-negative bacteria) elicit a host immune response and initiate the release of pro-inflammatory mediators such as cytokines to cause local inflammation. The cytokines and prostaglandins direct osteoclasts and fibroblasts to synthesize proteolytic enzymes

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that aid in the destruction of the structural integrity of the periodontium.[2] All the destructive factors collectively result in the formation of periodontal pockets (spaces or openings surrounding the teeth under the gum line) and bone loss which are considered as hallmarks in the progression of periodontitis.[3]

Clinical diagnostic tools such as gingival index (GI), plaque index (PI), probing pocket depth (PPD), clinical attachment level (CAL), and radiography provide insight into the severity of the disease, but to assess the disease progression, active sites of disease and to determine the response to a therapy biochemical tests targeting various biomarkers are essential. Saliva, the oral cavity fluid is a rich source of biomarkers for periodontitis.[4] The damaged periodontium releases various pro-inflammatory cytokines such as interleukins (ILs), prostaglandins and Tumor Necrosis Factor-alpha (TNF-alpha) which stimulate the synthesis of C-reactive protein (CRP) in liver.[5] CRP is an extremely sensitive marker of inflammation which reaches saliva through the gingival crevicular fluid (GCF) and its high levels in saliva are associated with chronic periodontitis.[6] Another such long-studied marker is aspartate aminotransferase (AST), an enzyme released in the GCF and saliva upon cytolysis of periodontal cells during periodontitis. Its increased activity in the GCF/saliva can be positively correlated with increased cytolysis of fibroblasts and gingival epithelial cells, making it a useful indicator in monitoring the state of infection.[7]

Periodontal therapy involves both surgical and nonsurgical procedures for effective treatment. The very first approach to treatment is the removal of bacterial plaque via nonsurgical procedures such as scaling and root planing (SRP). This commonly used restorative technique involves the removal of plaque, tartar, and bacterial by-products followed by smoothening of root surfaces. It has been noted that the incorporation of systemic antimicrobial agents in conjugation with SRP can provide improved outcomes when compared with SRP alone in terms of decreasing PPD and improving CAL.[8] A number of anti-microbials and chemotherapeutics agents have been used to treat periodontitis but are reported to have many side effects. Hence, as more and more natural remedies are being scientifically validated and proven to be safer than the synthetic drugs, a marked shift from modern drugs to natural remedies has been observed. The use of dietary ingredients as medicines is on the rise and fruits which possess excellent anti-microbial, anti-inflammatory, anti-septic, and anti-collagenase activities are being used as a complementary approach to achieve promising curing effects.

Natural drugs are now available in a number of local drug delivery forms such as mouth rinses, gels, creams, pastes, patches, films, and strips which have several advantages over systemic drug administration such as targeting directly the diseased area while causing negligible systemic side effects and bypassing bacterial resistance and drug interaction with other systemically taken drugs.[9]

For a long time, berries have been recognized as a rich source of bioactives with a broad spectrum of activities such as anti-inflammatory, anti-bacterial, anti-oxidant, anti-viral, and anti-cancer among others.[10] The American cranberry (*Vaccinium macrocarpon*), a native North American pulpy fruit consumed as fresh or dried fruit or juice, has demonstrated excellent efficacy in the treatment of various ailments. Polyphenolic phytoconstituents of cranberry possess strong efficacy against periodontal pathogens and are known to reduce the bacteria-mediated degradation of indigenous proteins like collagen and transferrin thereby preventing tissue destruction.[11] Another berry, *Garcinia cambogia*, commonly known as brindle berry is used as a weight-loss supplement, especially in people suffering from Type-2 diabetes mellitus. It contains hydroxycitric acid (HCA), a phytoconstituent exhibiting potent anti-oxidant and anti-inflammatory properties besides terpenoids, tannins, and other phenolic substances.[12,13] The beneficial properties of both berries warrant their use in periodontitis. Hence, the present study explores the protective activity of a polyberry gel containing phytoconstituent-enriched extracts of *V. macrocarpon* and *G. cambogia* in patients with periodontitis.

MATERIALS AND METHODS

Dried cranberries were sourced from an authentic supplier in Mumbai, India. The *Garcinia cambogia* extract (GCE) and HCA were obtained from Pharmanza Herbals Pvt. Ltd., India. Ferulic acid (FA) was purchased from Sigma Chemical Co., St Louis, MO, USA. Periodontal Plus AB (collagen fibril-based formulation containing tetracycline hydrochloride (2 mg of tetracycline) in 25 mg of collagen fibrils) was procured from Advanced Biotech Products Private Ltd., India. All other chemicals were of analytical grade and procured from authentic sources.

Cranberries were powdered mechanically and subjected to sonicator-assisted extraction using methanol and water in the ratio 80:20 v/v as solvent. The suspension obtained was centrifuged (10 min, 5000 rpm, 4°C), the supernatant was collected and evaporated to get a dark red-colored residue which was dried and stored in tight-mouthed containers in refrigerated conditions for further use. This was termed cranberry methanolic extract (CME). CME and GCE were dispersed in a carpool base along with other ingredients to make a gel [Table 1].[14] The formulated gel was filled in syringes and stored in refrigerated conditions for further use [Figure 1].

The analysis of CME and GCE was carried out using the CAMAG HPTLC system, Hamilton syringe as the applicator, and the CAMAG TLC scanner III with win CATS software (V

Table 1: Composition of polyberry gel

Ingredients	Quantity (g)
Carbopol 971P NF (g)	1.5
Sodium saccharine (g)	0.1
Sodium CMC (g)	0.5
Polyethylene glycol 400 (mL)	2
Triethanolamine (mL)	q.s.
Sodium benzoate (g)	0.5
CME (g)	2.5
GCE (g)	2.5
Distilled water	q.s.–100 mL
Total	100 mL

Sodium CMC – Sodium carboxymethyl cellulose; CME – Cranberry methanolic extract; GCE –*Garcinia cambogia* extract; q.s. – Quantity sufficient

Figure 1: Polyberry gel

1.44 CAMAG). Chromatographic separation of FA from CME and HCA from GCE was carried out on silica gel aluminum plates (silica gel 60 F254; 20 cm × 10 cm, Merck) using a mobile phase comprising Toluene: Ethyl Acetate: Methanol: Formic Acid (8:2:1:0.5 v/v/v/v). The detection was carried out at 293 nm to quantify both constituents. The amount of FA and HCA in the extracts was calculated from the calibration curves.

A combination of CME and GCE (1:1) was analyzed for total phenolic content by the method of McDonald *et al*. using gallic acid as standard.[15] From the standard curve, the concentration of gallic acid in the extract was obtained and results were expressed as gallic acid equivalents (mg/ml). The antioxidant content of the extracts was estimated by the (α, α-diphenyl-β-picrylhydrazyl) DPPH radical scavenging assay by the method of Rauf *et al*. using quercetin as standard and the results were expressed as percentage radical scavenging activity.[16] The ascorbic acid assay was carried out on the extracts by the 2, 4-dinitrophenyl hydrazine colorimetric method.[17]

The gel formulation was prepared; packed in collapsible tubes and subjected to stability studies at ± 25°C/60%Relative Humidity (RH) for 3 months as per ICH Q1A (R2) guidelines.[18] Samples were evaluated for viscosity, pH, and physical appearance on Day-0, Day-30, and Day-90. The texture analysis of the formulated gel was done using a Brookfield CT3 texture analyzer. The principle of the texture analyzer is to apply tension as well as compression forces on a sample using a probe. The resistance of the sample to these forces is measured by a calibrated load cell which is expressed in g or Newton.

For *in vitro,* permeation studies an appropriate section of the pig mucosa was mounted in a Franz diffusion cell. Tissue disks were equilibrated for 1 h at 37°C adding phosphate buffer saline (PBS) in both the donor and the acceptor compartments. The polyberry gel (0.5 g in 1.0 mL of buffer solution simulating natural human saliva) was placed in the donor compartment and PBS was placed in the acceptor compartment of the cell. At regular time intervals (60 min), aliquots were withdrawn from the acceptor compartment and the sample volume taken out was replaced by fresh PBS. The experiment was carried out for 6 h. The integrity of the mucosal tissue was monitored before and after the permeability study. The aliquots were analyzed by HPTLC for the active constituents FA and HCA.

Clinical studies

This study was a comparative clinical evaluation of the efficacy of the local drug delivery of the polyberry gel versus tetracycline fibers in the management of chronic periodontitis. It was a prospective single-blind, case–control, and single-centric clinical study. Patients with chronic periodontitis were selected from the outpatient department of Periodontics. The study protocol was approved by the Institutional Ethics Committee registered with the Dental College and Hospital. Written consent was taken before the study from all the participants and if the patient wanted to discontinue the treatment procedure during the study, he or she was allowed to do so.

Inclusion criteria and exclusion criteria

Healthy individuals suffering from chronic periodontitis with PPD of up to 5 mm, with no systemic diseases from the age group of 30–50 years were included in the study. On the other hand, patients suffering from diabetes, hypertension, or under medication for other systemic diseases or allergic to tetracycline, and pregnant/lactating women were excluded from the study.

Following was the clinical study design

Patients selected for the study were randomized and assigned to various groups and treatments with 21 patients in each group as follows**:**

1. Group A: Patients were treated with SRP
2. Group B: Patients were treated with SRP followed by subgingival placement of the polyberry gel (1 g)
3. Group C: Patients were treated with SRP followed by packing saline-soaked tetracycline fibers into the periodontal pockets with a cotton forceps or curette until the pocket was filled up to or slightly below the gingival margin.

Following the initial examination, the selected subjects underwent SRP. After 4 weeks, only those patients maintaining optimum oral hygiene with persistent isolated periodontal pockets were selected for further placement of gel/tetracycline fibers. The area to be operated was anesthetized by administration of lignocaine (2%) and adrenaline in a concentration of 1:200,000 followed by the curettage of the area. The polyberry gel/tetracycline was placed subgingival and the area was protected and covered with noneugenol (Coe Pak) periodontal dressing. Postoperative instructions to the treated patients included maintenance of self-oral hygiene and timely consumption of prescribed antibiotics. Saliva was collected from the patients on the 1st day of the procedure and again after 1 month and subjected to evaluation of salivary parameters.

The clinical parameters namely, PI, GI, PPD, and CAL were recorded at baseline and again after 1 month using a periodontal probe. The estimation of CRP from saliva was done by latex slide test using a standard agglutination test kit procured from Spectrum Diagnostics, Egypt. The estimation of another salivary parameter, AST was done using a biochemical test kit supplied by Erba, India. For biochemical analysis, the test samples were taken in triplicate for accuracy and reproducibility.

Statistical analysis

For clinical parameters, the normality of numerical data was checked using Shapiro–Wilk test. Since the data did not follow a normal curve nonparametric tests were used for comparisons. Inter-group comparison (>2 groups) was done using Kruskall–Wallis test followed by pairwise comparison using Mann Whitney *U*-test. The intra-group comparison was done using Friedman's test (for >2 observations) followed by pairwise comparison using Wilcoxon Signed–rank test. For salivary parameters, all values were expressed as mean ± standard deviation from 21 patients in each group. Results were statistically analyzed using one-way analysis of variance followed by the Tukey–Kramer multiple comparison test; $P < 0.05$ was considered statistically significant. GraphPad InStat version 4.00 of Graph Pad Software Inc., San Diego, California, USA, was the software used for this statistical analysis.

RESULTS

Quantification of FA in CME and HCA in GCE by HPTLC: The content of FA in CME (100 mg) was 0.86 µg and HCA in GCE (100 mg) was 7.70 µg, as calculated from the calibration curves. [Figure 2a-d] represents the HPTLC fingerprinting of standard FA, FA in CME, Standard HCA, and HCA in CME.

Phenolic content, total antioxidants, and ascorbic acid in CME and GCE: The total phenolic content of the extracts was determined to be 37 mg GAE/g. The IC50 Value of DPPH Radical Scavenging Activity for quercetin was found to be 21.55 ppm and for the combined extracts was 25.95 ppm. The ascorbic acid content of the combined extracts was 5.32 g/dL.

Stability study, texture analysis, and *in vitro* permeation study of the gel: The values of all the parameters evaluated under

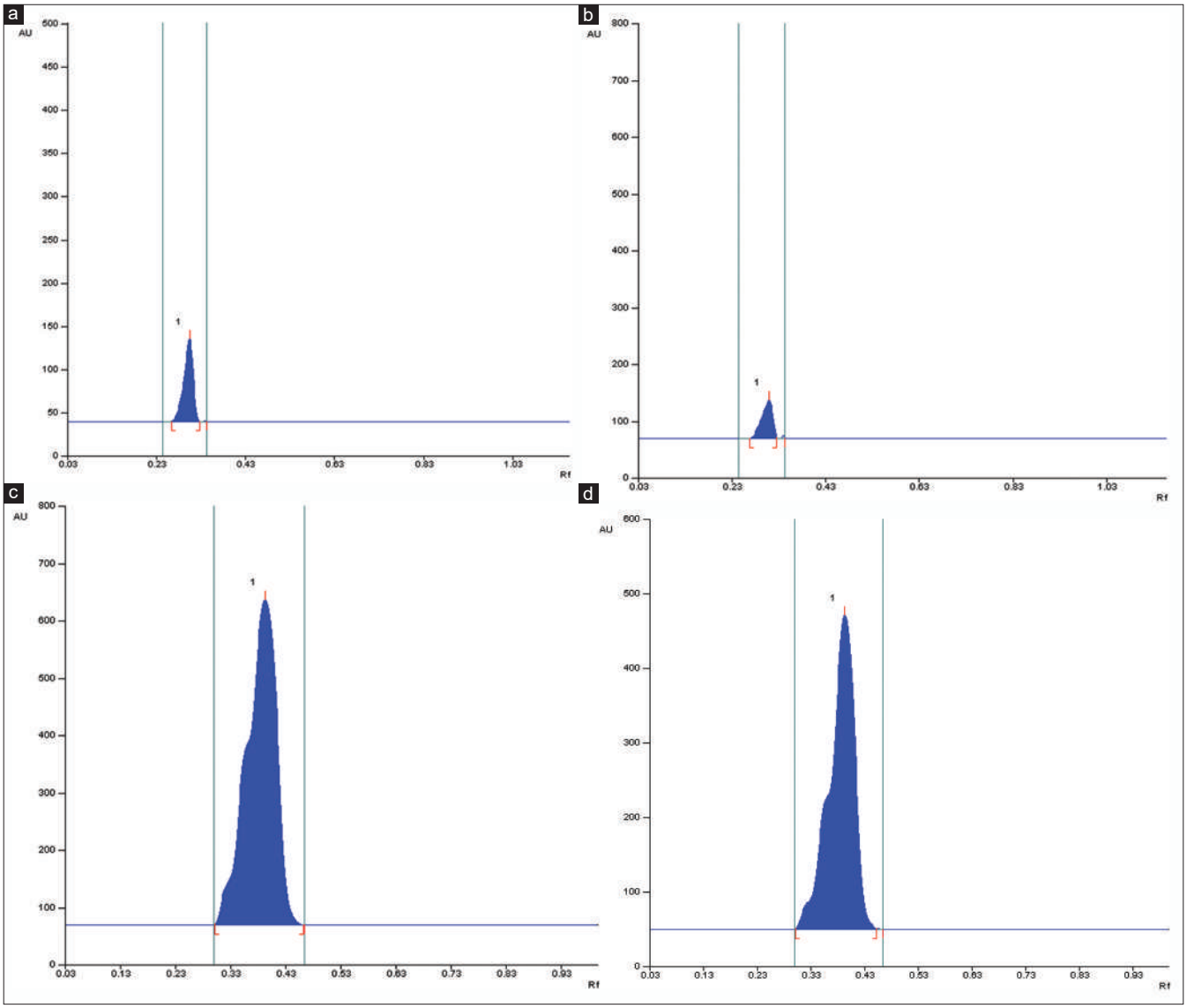

Figure 2: (a) HPTLC finger printing of standard FA at 293 nm. (b) HPTLC finger printing of FA in CME at 293 nm. (c) HPTLC finger printing of standard HCA at 293 nm. (d) HPTLC finger printing of HCA in GCE at 293 nm. FA – Ferulic acid; Rf – Retention factor; AU – Area under the curve; CME – Cranberry methanolic extract; HCA – Hydroxycitric acid. HPTLC – High performance thin layer chromatography; GCE – *Garcinia cambogia* extract

stability studies are shown in Table 2 and those for texture analysis are listed in Table 3.

The polyberry gel may be considered to be stable for use at least up to 3 months. Further optimization studies are required for use beyond 3 months.

The *in vitro* permeation studies revealed that the maximum release of HCA as well as FA was between the 2nd and 3rd h of the study. Figure 3a depicts the graphical representation of permeation studies of HCA while Figure 3b is the graph of permeation studies of FA.

Evaluation of clinical parameters

The effect of SRP, polyberry gel, and tetracycline fibers on clinical parameters intra-group and inter-group is depicted in Table 4. Intra-group comparison of PI, GI, CAL, and PPD showed significant ($P < 0.01$) improvement after a month as against the baseline values as depicted in [Figure 4a-i]. There was a significant ($P < 0.01$) difference in PI, GI, CAL, and PPD values when Group A was compared to Group B as well as Group C, while a nonsignificant difference was seen between Group B and Group C.

Evaluation of AST and CRP: Polyberry gel and tetracycline-treated groups of patients showed a significant attenuation of the periodontitis-elevated AST and CRP levels when compared with the SRP-treated group at the end of 1 month [Figure 5a and b].

DISCUSSION

In diseases such as periodontitis where progression is mediated through biological membranes, the concept of mucoadhesion has been introduced to aid drug delivery by modifying tissue permeability, increasing drug bioavailability, and reducing the

Table 2: Stability studies of polyberry gel

Time points	Color and homogeneity	Consistency, clarity	pH	Viscosity in P (poise)
Day-0	Light yellow, homogenous	Good, clear	6.76	10.5
Day-30	Light yellow, homogenous	Good, clear	6.12	10.13
Day-90	Light yellow, homogenous	Good, clear	6.68	9.92

Table 3: Texture analysis of polyberry gel

Time period (month)	Hardness cycle (g)	Deformation at hardness (mm)	Load at target (g)	Adhesiveness (mJ)
0	58	14.92	58	1.50
3	61	14.93	61	0

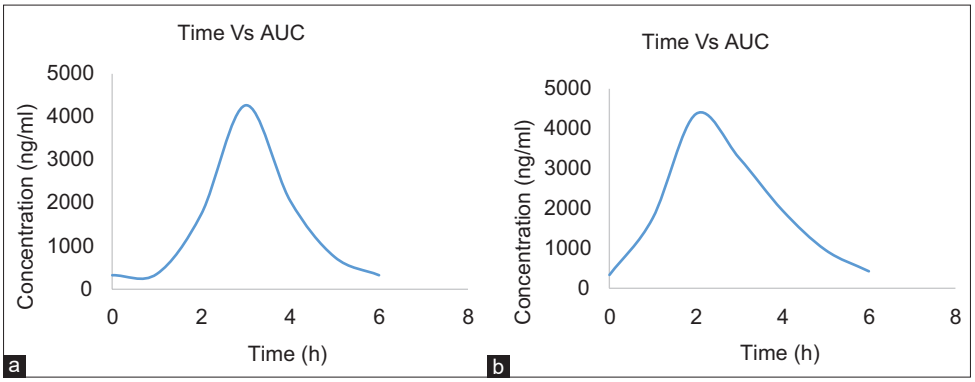

Figure 3: (a) Graphical representation of permeation studies of HCA. (b) Graphical representation of permeation studies of FA. FA – Ferulic acid; HCA – Hydroxycitric acid; AUC – Area under the curve

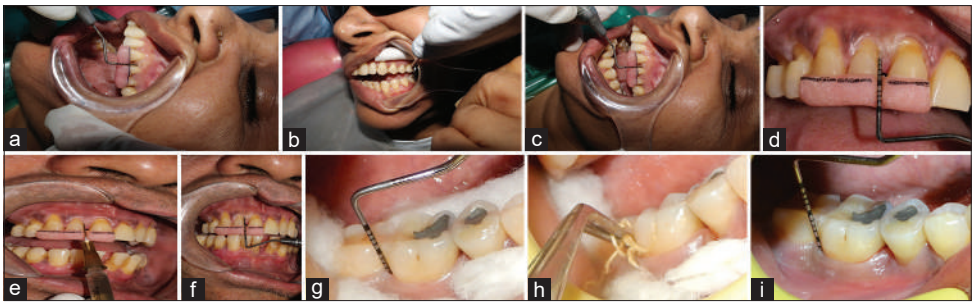

Figure 4: (a-c) Represent clinical pictures of baseline PPD, PPD after scaling and postoperative PPD after one month respectively of Group A (SRP). (d-f) Represent clinical pictures of baseline PPD, application of polyberry gel in the pocket and postoperative PPD after one month of gel placement respectively of Group B (Polyberry Gel). (g-i) Represent clinical pictures of baseline PPD, placement of tetracycline fibres and postoperative PPD after one month of tetracycline placement respectively of Group C (Tetracycline fibres). PPD – Probing pocket depth; SRP – Scaling and root planning

Table 4a: Effect of scaling and root planing, polyberry gel and tetracycline fibres on plaque index, gingival index, probing pocket depth and clinical attachment level: Intra group comparison of outcome variables for Groups A, B and C

Groups	Time interval	PI	GI	PPD	CAL
Group A	Baseline	2.48±0.51	2.52±0.51	5±0.71	5.29±0.90
	One month	1.43±0.51**	1.57±0.60**	4.19±0.75**	4.43±0.81**
Group B	Baseline	2.67±0.48	2.52±0.51	4.95±0.67	4.9±0.77
	One month	0.67±0.66**	0.81±0.68**	2.81±0.75**	2.76±0.89**
Group C	Baseline	2.48±0.51	2.52±0.51	4.76±0.77	4.76±0.83
	One month	0.62±0.59**	0.62±0.74**	2.38±0.59**	2.43±0.68**

***P*<0.01 is statistically significant difference. All values are mean±SD. Group A – SRP; Group B – SRP+Polyberry gel; Group C – SRP+Tetracycline fibres. PI – Plaque index; GI – Gingival index; PPD – Probing pocket depth; CAL – Clinical attachment level; SD – Standard deviation; SRP – Scaling and root planning; *P* – *P* values

Table 4b: Effect of scaling and root planing, polyberry gel and tetracycline fibres on plaque index, gingival index, probing pocket depth and clinical attachment level: Inter group comparison of outcome variables between each pair of group

Dependent variable	Group comparison	PI (*P*)	GI (*P*)	PPD (*P*)	CAL (*P*)
Baseline	A-B	0.218#	1.000#	0.823#	0.206#
	A-C	1.000#	1.000#	0.278#	0.078#
	B-C	0.218#	1.000#	0.353#	0.513#
1 month	A-B	0.000**	0.001**	0.000**	0.000**
	A-C	0.000**	0.000**	0.000**	0.000**
	B-C	0.866	0.323	0.049*	0.207

***P*<0.01 and **P*<0.05 is highly statistically significant difference; #*P*>0.05 is statistically nonsignificant difference. All values are mean±SD. Group A – SRP; Group B – SRP + Polyberry gel; Group C – SRP + Tetracycline fibres. PI – Plaque index; GI – Gingival index; PPD – Probing pocket depth; CAL – Clinical attachment level; SD – Standard deviation; SRP – Scaling and root planing; *P* – *P* values

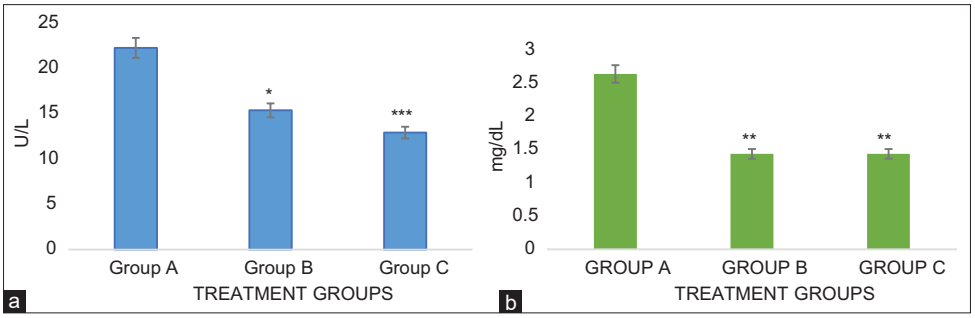

Figure 5: (a) Effect of SRP, polyberry gel and tetracycline fibres on AST. All values are expressed as mean ± Standard deviation; *n* = 21 in each group; One-way ANOVA followed by Tukey–Kramer *post hoc* test is applied for statistical analysis; **P* < 0.05 and ****P* < 0.001 when gel (Group B) and tetracycline group (Group C) compared with SRP (Group A). (b) Effect of SRP, polyberry gel and tetracycline fibres on CRP. All values are expressed as mean ± Standard deviation; *n* = 21 in each group; One-way ANOVA followed by Tukey–Kramer *post hoc* test is applied for statistical analysis; ***P* < 0.01 when gel (Group B) and tetracycline group (Group C) compared with SRP (Group A). SRP – Scaling and root planning; AST – Aspartate aminotransferase; CRP – C-reactive protein

frequency of administration. The drug is often dispersed into a polymeric material, which when in contact with the mucosal medium, acts as an adhesive drug-carrying system.[19] Hence, a mucoadhesive polyberry gel which is appropriate to cure periodontitis was formulated and used in this study.

Novel therapeutic approaches for periodontitis include preventive plaque control measures and natural adjunctive treatments. Fruits comprise natural phytochemicals and are highly effective substitutes for antibiotics, hence, signify an alternative approach in the preventive and therapeutic management of oral and periodontal infections.[20] The incorporation of berry fruits which are rich sources of flavonols, anthocyanins, and proanthocyanidins (PACs) in dental formulations can be an effective means to treat periodontitis. These active compounds can inhibit the formation of bacterial biofilms and exhibit strong antioxidant and anti-inflammatory effects.[21]

The present study has evaluated and compared the effectiveness of a novel polyberry fruit gel with the commonly used tetracycline fibers. The efficacy of the active phytoconstituents of the berries in the present study was evident with the polyberry gel producing comparable results with tetracycline fibers in ameliorating periodontitis. The probable mechanism of action could be the potent antioxidant activity of the gel's phenolic phytoconstituents as evidenced in the DPPH-α, α-diphenyl-β-picrylhydrazyl radical scavenging assay, which led to amelioration of periodontitis in many ways. Polyphenolic acids such as FA promote the proliferation and migration of human oral fibroblasts which secrete the dental matrix to reconnect the tooth root, gingiva, and periodontal ligament bringing about periodontal restoration.[22] FA by virtue of its powerful antioxidant activity may also attenuate oxidative stress-induced inflammation to help periodontal wound healing. Since it is a major phenolic component of cranberry, it was quantified in CME and used in permeation studies as a

marker. The PACs of cranberry are reported to interfere with the formation of bacterial biofilms by means of their anti-proteinase activity.[23] A PAC-rich-fraction has been shown to block the production of matrix metalloproteinases (MMPs) by fibroblasts and macrophages, inhibit secretion of ILs by host cells and curtail osteoclast differentiation into bone-resorbing cells.[24] MMPs are enzymes that orchestrate tissue destruction and evoke immune responses leading to periodontal inflammation. Cranberry is an excellent source of ascorbic acid (Vitamin C), a strong scavenger of excessive free radicals. Ascorbic acid prevents the progression of periodontal disease by inducing the differentiation of periodontal ligament progenitor cells.[25] Thus, it was assayed and also used as a determinant of the antioxidant activity of the gel. While PACs of cranberries may interfere with bacterial adhesion and formation of bacterial biofilm, HCA, the principal active constituent of brindleberry has the efficacy to inhibit mediators of inflammation.[26] Hence, it was quantified in GCE. The cumulative effect of both the berries could be seen in the study.

PI is an *index* to measure dental *plaque* that occurs in the areas adjacent to the *gingival* margin and the border of the gum surrounding, but unattached to the teeth. Attenuation of the plaque formation by the herbal constituents may have been responsible for the significant decrease in PI, both inter-group and intra-group over the study period, verifying antibacterial action of the polyberry gel. GI is a strong indicator of periodontal disease that measures the magnitude of inflammation, edema, and bleeding on gentle probing of the gums. The reduction in GI in the gel-treated groups when compared with the SRP group may be due to a potent anti-inflammatory activity of the phytoconstituents. The PACs and polyphenols of the gel probably inhibit nuclear factor-κB and MMP-3 production by the gingival fibroblasts to curtail inflammation.[27] Furthermore, the bacterial lipopolysaccharide-evoked IL-6, IL-8, and PGE-2 responses from gingival fibroblasts resulting in severe inflammation and aggravation of periodontitis were possibly inhibited by the gel's phytoconstituents.[28] CAL, a measurement of the extent of periodontal support is defined as the loss of connective tissue adherence leading to the detachment of collagen fibers from the cemental surface of the tooth's root. It is the primary manifestation of periodontitis. The destruction of gingival fibers and fibers of the periodontal ligament and their detachment from the tooth's root leads to the migration of the junctional epithelium to the surface of the root, and the alveolar bone no longer supports the tooth.[29] SRP treatment by means of smoothening the tooth surface helps in the reattachment of gum tissue decreasing CAL. PPD is the distance measured from the base of the pocket to the most apical point on the gingival margin and is a measure of the patient's ability to maintain proper plaque control. Probing depths of more than 3 mm require periodontal intervention. CAL and PPD measure periodontal destruction by using a straight probe graduated in millimeters. Significant amelioration of CAL was noted in patients treated with the polyberry gel. The constituents of cranberry are reported to attenuate adherence of oral pathogens to mucosal surfaces in the mouth and promote dissociation of co-aggregation of periodontopathogens by means of their potent anti-adhesion activity, thus bringing about an additional reduction in PPD.[30] Polyphenols and PACs are known to increase the cross-linking of collagen, the main component of the connective tissue, making it strong and resistant to degradation, thus decreasing the detachment of collagen fibers from the root surface, and decreasing CAL.[31]

Periodontal studies reported hitherto describing inhibition of bacterial adhesion or host inflammatory molecules by polyphenolic acids/PACs have all been conducted by *in vitro* techniques. More studies on bioactive components of cranberry as well as brindleberry, including *in vivo* metabolism and bioavailability are necessary to determine the clinical applications of these compounds. Contemporary research is directed at developing more physiologically acceptable and commercially feasible drug delivery systems to act as adjuncts to the surgical as well as the nonsurgical treatment approaches for periodontal infections. This study is an example of a polyphenol-rich local drug delivery system which was evaluated *in vivo* for use as adjunct to SRP. As a continuation, analysis of biochemical parameters such as inflammatory markers (Fibronectin, TNF-alpha and IL-1), lactoferrin, MMP 8, and antioxidants among others, as well as pharmacokinetic studies could be carried out to understand the mechanisms of action of the polyberry gel in ameliorating periodontitis.

CONCLUSION

It may be concluded that the polyberry gel showed a significant reduction in periodontitis when compared with SRP alone and was comparable with the standard tetracycline. The potent antibacterial, antioxidant, and anti-inflammatory activities of its phytoconstituents may be responsible for this effect. More clinical data are warranted to establish herbal medications as effective and reliable treatments for periodontal therapies.

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Conflicts of interest

There are no conflicts of interest.

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