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Research Article

PIPER BETLE L AS A ANTI-INFLAMMATORY AGENT

Bharathi Poojary[1]., Leena Shettar[2]., Dhiraj J Trivedi[3]., Kishore G Bhat[4]., Swati Setty[2] and Srinath L Thakur[2]

[1,2]Department of Periodontics, SDM Dental College and Hospital, Sattur, Dharwad-580009, Karnataka
[3]Department of Biochemistry, SDM Medical College and Hospital, Sattur, Dharwad-580009, Karnataka
[4]Department of Microbiology, Maratha Mandal's NGH Institute of Dental Sciences & Research Centre, Bauxite Road, Next to KSRP Ground, Belgaum-590010

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ABSTRACT

Introduction: Piper betle (L) is a common plant cultivated in Asian countries, leaves of which are used in folk medicine for the treatment of various disorders.
Aim: To evaluate the anti-bacterial efficacy of 4% Piper betle (L) leaves extract mouth rinse on the Human Gingiva.
Materials and Methods:45 systemically healthy patients,15 years and above with mild to moderate Gingivitis were randomly divided into:
Group A: Distilled Water (Placebo).
Group B: Commercially available 0.2% Chlorhexidine gluconate (Positive Control).
Group C: 4% Piper betle leaves extract mouth rinse (Test Group).
The supra-gingival plaque samples were collected at baseline and 15 days and Colony Forming Units (CFU) were recorded. Plaque Index(PLI), Gingival Index (GI) and Sulcus Bleeding Index(SBI) were recorded at baseline,7th day and 15th day, thorough scaling was done at baseline, then provided with the mouthrinse depending on which group they belonged .Statistical analysis was done using Kruskal-Wallis, Mann-Whitney and the Wilcoxon matched tests.
Results: Test group showed significant reduction in PLI, GI, SBI at 7th and 15th day compared to baseline values.
Conclusion: The present study demonstrated the anti-inflammatory efficacy with 4% aqueous extract of *Piper betle linn*.

INTRODUCTION

Dental plaque is one of the etiological agent in causation of gingival and periodontal disease. Dental plaque has been proved by extensive research of Harold Loe to be a paramount factor in initiation and progression of gingival and periodontal disease. Removal of this dental plaque is very important in prevention of gingival and periodontal disease[1].

The various procedures of removal of the dental plaque include mechanical and chemical means. Mechanical methods include professional means by scaling and rootplaning and at home by tooth brushing. But the mechanical methods have limitations like their effectiveness depends on the skill and technique of operator and the individual .Many individuals find it difficult to maintain adequate levels of plaque control at many sites which has led to the use of chemical means of plaque control as an adjunct to the mechanical method. Various mouth rinses are available today which target at the reduction of this plaque formation and thereby reduce disease causation. One of the commonly used mouthrinses is the Chlorhexidine gluconate which has been considered as the gold standard for prevention of dental plaque. But Chlorhexidine has certain side effects like staining of teeth ,alteration of taste sensation. Hence a need is felt for an alternative medicine that could provide a product already enmeshed within a traditional Indian set up and is also safe and economical[2].

Herbs are plants with medicinal properties. Herbs are used to cleanse the blood, warm and stimulate the body, increase surface circulation, increase elimination of wastes, reduce inflammation, and calm and soothe irritation. Herbs may be used internally as pills, syrups, and infusions, or externally as poultices, plasters, and liniments. A topical application of clove

Corresponding author:* **Bharathi Poojary
Department of Periodontics, SDM Dental College and Hospital, Sattur, Dharwad-580009, Karnataka

oil, for instance, will stop the pain of toothache. Moist herbal wraps, either hot or cold, can be used on specific affected parts of the body[3].These are naturally available sources which can be put to beneficial use once adequately researched. These are also believed to be least harmful to human health. The beneficial properties of garlic, tea tree oil on the periodontium are well documented[4]. Piper betle L., (Piperaceae) has been extensively used in traditional herbal remedies in India, China, Taiwan, Thailand and many other countries. It is reported for various pharmacological activities such as antimicrobial, antioxidant, antimutagenic, anticarcinogenic, antiinflammatory properties [5]. It also acts as a stimulant, a breath freshener, a carminative, a sialagogue, a cardiac tonic, a pain killer in joint pain, an aphrodisiac, an astringent, an antiseptic , a digestive and pancreatic lipase stimulant , wound healing [5-7].

Piper betle L. is a common plant cultivated in Asian countries, leaves of which are used in folk medicine for the treatment of various disorders. *Piper betel* L. belongs to the family Piperaceae. This family usually contains herbs or shrubs often with swollen nodes, usually aromatic. The leaf is pungent, bitter, sweetish, acrid, heating, carminative, stomachic, anthelmintic, tonic, aphrodisiac and laxative. The leaves are useful in cough, foul smell in the mouth, ozoena, bronchitis, elephantiasis of the leg; improves appetite, it improves taste and appetite, tonic to the brain, heart, liver, strengthens the teeth, lessens thirst, clears the throat, vulnerary and styptic. The juice of the leaves is dropped into the eye in night blindness. The essential oil from the leaves is used in the treatment of catarrhal disorders and as an antiseptic. The decoction of leaves used for heating wounds. The fruit is employed with honey as a remedy for cough[5].The extracts of piper betle plant has been reported to posses many biological activities that have contributed to their role in development of therapeutic products (Nair and Chanda,2008;Wirotesangthong *et al* 2007)[8,9]. Piper betle is commonly used as traditional medicine as it posses antioxidant, antibacterial, antifungal, antidiabetic, and radioprotactive activity (Wirotesanthong *et al* 2007)[6]. In perspective of oral health maintainance the aqueous extracts of Piper betle has showed positive antiplaque activity that act on dental plaque. These extracts reduce the adhering capacity of the acquired pellicle which forms on the tooth surfaces at early phase of plaque formation to receive and bind the bacteria (Fathilal and Rahim 2003) and second by diminishing the cell surface hydrophobicity of bacteria which are required to assist the adherence process (Fathilah *et al* 2006)[10].

With these properties in mind, the authors conducted a study with the aim to evaluate the anti bacterial efficacy of the new herbal mouthrinse containing *Piper betle* L. leaves extract on Gingival health.

MATERIALS AND METHODS

Fresh leaves of *Piper betle* L. were collected from the local market. The authentication was done by the biochemistry department of our college. The leaves were washed first with tap water followed by distilled water and air dried by spreading on filter paper in shade. Preparation of Piper betle extract and mouthwash- Dry leaves of the *Piper betle* L. were crushed to prepare fine paste.50gm of fine paste was added to around 100ml distilled water. The mixture of paste and distilled water were homogenized with high speed blender. Care was taken to maintain the temperature below 15^0 C by providing cold water bath. 100 ml more distilled water was added and once again subjected for homogenization. The so obtained homogenized paste was then filtered with muslin cloth by squeezing. 28gm of remnant leave paste was discarded. 222 ml of liquid extract was obtained after the above procedure. The liquid extract was then centrifuged at 5000RPM for 10 min at 6degree Celsius to remove any suspended particle. The supernatant was collected in sterile glass container and stored at refrigerated condition. The aqueous extract contained 11gm% extractive from the paste. This was considered as 100% extract for MIC activity.

Further dilutions were prepared from the above 100% extract and mouthwash was prepared. The mouthwash was prepared in two different concentrations 2% and 4% .The efficacy of the both(2 % and 4 %) mouth rinse checked microbiologically for their MIC.

MIC procedure - 9 dilutions of each percentage of mouthwash was done with BHI for MIC. In the initial tube 20microliter of mouthwash was added into the 380microliter of BHI broth. For dilutions 200microliter of BHI broth was added into the next 9 tubes separately. Then from the initial tube 200microliter was transferred to the first tube containing 200microliter of BHI broth. This was considered as 10^{-1} dilution. From 10^{-1} diluted tube 200microliter was transferred to second tube to make 10^{-2} dilution. The serial dilution was repeated up to 10^{-9} dilution for each percentage of mouthwash. From the maintained stock cultures of required organisms, 5microliter was taken and added into 2ml of BHI (brain heart infusion) broth. In each serially diluted tube 200microliter of above culture suspension was added. The tubes were incubated for 24 hours and observed for turbidity[11].

From the MIC results it was evident that out of the two percentage mouthwash prepared that is 2% and 4%, 4 % extract showed better antibacterial properties.

Palatability and adverse effects of both 2% and 4% mouthwash were checked on 10 volunteers. No adverse effects were detected with both 2% and 4% mouthwash.4% extract was selected for further study since it showed better antibacterial properties when compared to 2%.

A total of 45 systemically healthy patients, 15 years and above with mild to moderate Gingivitis were included in this study. Informed consent taken. They were randomly divided into 3 groups:

Group A: Distilled Water (Placebo).
Group B: Commercially available 0.2% Chlorhexidine gluconate (Positive Control).
Group C: Mouthrinse containing 4% Piper betle leaves extract (Test Group).

The subjects were informed about the study and consent was taken. Once the patient satisfied the inclusion criteria, supragingival plaque sample was collected in a sterile ependoff tube containing 500 µl of RTF. The scaling and root planing of each subject was then done by a single trained operator. The subjects were then dispensed the respective mouthrinses depending on the group to which they belonged. They were given brushing instructions and also instructions for the use of the mouthrinse. The patients were asked to rinse the

mouth twice daily with the respective mouthwashes. Subjects were recalled on the 7th day and later on the 15th day for re-evaluation.

The following parameters were evaluated at baseline, 7th day and 15th day recall visits:

1. Plaque index
2. Gingival index
3. Sulcus bleeding index.

The plaque samples were collected at 15 day and CFUS were evaluated.

Statistical analysis

Statistical analysis was done using Kruskal-Wallis ,Mann-Whitney and the Wilcoxon matched paired tests.

RESULTS

The MIC results showed that 4% Piper Betle L. mouthwash was effective microbiologically [I].

When a comparison was made between Group A (placebo) and Group B(Chlorhexidine) the reduction in the PLI,GI was seen from baseline to 7th and 15th day which was not statistically significant. Similar results were observed when group A(Placebo) was compared to group C*(Piper Betle L.)* Also when comparison was done between group B(Chlorhexidine) and group C(*Piper betle L.*) a difference was found but this difference was not statistically significant.

When a comparison was made between Group A (placebo) and Group B(Chlorhexidine) the reduction in the SBI was seen from baseline to 7th and 15th day which was statistically significant. Similar results were observed when group A(Placebo) was compared to group C*(Piper Betle L.)* Also when comparison was done between group B (Chlorhexidine) and group C (*Piper betle L.*) a difference was found but this difference was not statistically significant[II].

The Colony Forming Unit showed reduction from baseline to 15th day in all 3 groups. When a comparison was made between the groups a reduction was seen but it was not statistically significant.

MIC- Results of the 2 different mouthwash concentrations 2% and 4%

S. Mitis	500	250	125	62.5	31.25	16	8	4	2	1
2%	S	R	R	R	R	R	R	R	R	R
4%	S	S	S	R	R	R	R	R	R	R

Aa	500	250	125	62.5	31.25	16	8	4	2	1
2%	S	S	S	S	S	S	S	S	S	R
4%	S	S	S	S	S	S	S	S	S	S

Note-S- Sensitive
R- Resistant

Sulcus Bleeding Index

Sulcular bleeding index at baseline						
PIPER BETLE	15	2.27	2.00	0.59	7.23	**0.02 (S)**
CHLORHEXIDINE	15	1.80	2.00	0.41		
PLACEBO	15	2.20	2.00	0.41		
Pairwise compariosn (Mann Whitney Test) for SBI						
Piper betle VS Chlorhexidine – p value 0.06(NS)						
Piper betle Vs Placebo – p value 0.64 (NS)						
Chlorhexidine Vs Placebo - p value 0.09 (NS)						

Sulcular bleeding index on 7th day						
PIPER BETLE	15	1.33	1.00	0.48	24.17	**< 0.001 (S)**
CHLORHEXIDINE	15	1.13	1.00	0.35		
PLACEBO	15	2.00	2.00	0.01		
Pairwise compariosn (Mann Whitney Test) for SBI						
Piper betle VS Chlorhexidine – p value 0.36 (NS)						
Piper betle Vs Placebo – p value 0.001 (HS)						
Chlorhexidine Vs Placebo - p value 0.001 (HS)						

Sulcular bleeding index on 15th day						
PIPER BETLE	15	1	1	0	32.00	**0.001 (S)**
CHLORHEXIDINE	15	1	1	0		
PLACEBO	15	1.8	2	0.41		
Pairwise compariosn (Mann Whitney Test) for SBI						
Piper betle VS Chlorhexidine – p value 0.99 (NS)						
Piper betle Vs Placebo – p value 0.001 (HS)						
Chlorhexidine Vs Placebo - p value 0.001 (HS)						

DISCUSSION

Natural products are in great demand due to its extensive biological properties and providing source for discovery of many types of effective bioactive compounds. In India *Piper Betle L.* is still regarded as an excellent mouth freshner and it is served on social, cultural and religious occasions like marriage, religious festivals[12].Also crude extract of *Piper betle* L. are among the plants that have been associated with the control of caries[13] and periodontal disease[14]and control of bad breath[15]. *Piper betle* L. has been recognized for their many Pharmacological activities such as its antioxidant and antibacterial properties[(16,17,18)]. Also in the betel leaves are also regarded as cheap, natural and easily available appetizer and refresher. It was found that the extract of *Piper Betle Linn* leaves contain fatty acids (stearic acid and palmitic acids) , hydroxy fatty acids esters (hydroxyl esters of stearic, palmitic and mystiric acids) and hydroxyl chavicol. Fatty acids can act as anionic surfactants and have antibacterial, antifungal properties at low ph ,in addition to being selective against gram positive organisms by targeting the structure and function of bacterial cell walls and membranes[(19-21)]. To our knowledge no vivo studies have been carried out. Hence we decide to do in vivo study of *Piper Betle L.* mouthwash to see the antinflammatory effect and antibacterial effect.

Taking into consideration of study done by Fathilah *et al* in 2003 we decided to prepare mouthwash between concentration of 2% and 4%.Our MIC results showed that out of the 2 different concentrations of 2% and 4% ,4% concentration of *Pier Betle L.* mouthwash was more effective microbiologically. Palatability and adverse effects of both 2% and 4% mouthwash were checked on 10 volunteers. No adverse effects were detected with both 2% and 4% mouthwash.4% extract was selected for further study since it showed better antibacterial properties when compared to 2%. After establishing the MIC we carried out a in vivo study in our institute to evaluate the efficacy of *Piper Betle L.* as mouthwash. The study

consisted of 45 systemically healthy subjects with moderate gingivitis who were randomly divided into 3 groups :Group A(Placebo),Group B (Chlorhexidine), GroupC (*Piper Betle L.*). At baseline, supragingival plaque samples of the subjects were collected and colony forming units(CFU) were recorded. Clinical parameters like plaque index(PLI)[22], gingival index(GI)[23] and Sulcus Bleeding Index(SBI)[24] were also recorded. All patients were subjected to scaling. At the same appointment ,the patients were provided with the mouthrinse depending on the group they belonged. On the 7th day and 15 day ,the patients were reviewed and the PLI[22],GI[23]and SBI[24] were recorded. On the day 15th the supragingival plaque samples of the subjects were collected and colony forming units(CFU) were recorded again.

The Plaque index(PlI) and the Gingival Index (GI) scores were reduced from the baseline to the 7th day but from 7th day to 15thday the scores remained the same in group A(Placebo). The reason for the reduction of the scores could be attributed to non-surgical therapy (scaling) which was done at baseline in this group. In the group B (Chlorhexidine) the PlI and GI scores reduced from baseline to 7th day and 15th day. The same results were observed in group C as well. This could be attributed to the antiplaque and antigingivitis effect of Chlorhexidine[10,25,26] and *Piper Betle L.* respectively[27]. The results of our study with respect *to Piper Betle L.* are similar to the results of the study conducted by Fathilah *et al*[26]. But they conducted an in vitro study.

The Sulcus Bleeding Index(SBI) scores were reduced from baseline to 7th day and 15th day in group A(Placebo) suggestive of effect of scaling. The same results were seen with respect to group B (Chlorhexidine) and group C(Piper Betle L.) which can be attributed to the anti-inflammatory effects of Chlorhexidine[10,25-27] and Piper Betle L[28]. Also when the scores of the groups were compared i.e group A with group B, group A with group C with respect to SBI statistically significant difference was seen. But when group B was compared with group C no statistically significant results were seen. The more reduction in the SBI was with Chlorhexidine then with *Piper Betle L.* when compared to placebo. The anti-inflammatory property of Piper Betle L. can be attributed to allylpyrocatechol (APC). Studies have reported that APC inhibited production of NO and PGE_2 in a dose dependent manner as also decreased mRNA expression of iNOS, COX-2, IL-12p40 and TNF-alpha. Sarkar *et al* in 2008 investigated the effects of APC on this transcription factor since nuclear factor-κB (NF-κB) appears to play a central role in transcriptional regulation of these proteins. APC inhibited LPS induced nuclear factor-kappaB (NF-κB) activation, by preventing degradation of the inhibitor kappaB (IκB). Taken together,the available data indicates that APC targets the inflammatory response of macrophages via inhibition of iNOS, COX-2 and IL-12 p40 through down regulation of the NF-κB pathway, indicating that APC may have therapeutic potential in inflammation associated disorders[29]. Investigation of the phytoconstituents of *Piper Betle* revealed the presence of phenolic compounds, chevibetol and allylpyrocatechol, and their respective glycosides in significant proportions[30].Since phenolics are reputed to be potent anti-inflammatory compounds (Surh *et al* 2001), it was expected that the phenolics identified in *Piper Betle* would contribute towards its anti-inflammatory activity[31]. In our study we have concentrated on SBI to show anti-inflammatory activity.

As per the results, all three groups have shown antibacterial activity which was demonstrated by reduction in the bacterial counts from baseline to 15thday .When the results of the groups were compared there was no statistically significant difference found. Hence the antibacterial activity of *Piper Betle L.* needs to be proven with more studies.

Piper Betle L. being a herb causes no harm to human health even when used daily and it is easily available and economical. There were no reported side-effects/complaints by any of the subjects all through the course of our study.

CONCLUSION

The present study demonstrated the anti-inflammatory efficacy with 4% aqueous extract of *Piper betle* linn. But the antibacterial activity of *Piper Betle L.* still needs to be proved. Further studies with a larger sample size are required.

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