The effect of *Frankincense* in the treatment of moderate plaque-induced gingivitis: a double blinded randomized clinical trial

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ABSTRACT

**Background and the purpose of the Study:** Extract of *Boswellia Serrata* species has been used in the Indian traditional medicine in the treatment of various inflammatory diseases. The present study was designed to evaluate anti-inflammatory effects of *Frankincense* in the treatment of gingivitis, which is a periodontal tissue inflammatory disease.

**Methods:** This double blind randomized placebo controlled trial was carried out among high school female students with moderate plaque-induced gingivitis. Based on either administration of 0.1 gram of *Frankincense* extract or 0.2 gram of its powder or placebo and whether the patients undergone scaling and root planning (SRP) or not, they were randomly assigned to 6 groups. The primary efficacy outcome was changes in Gingival Index (Loe & Sillness) and the secondary outcomes were alteration in plaque index (Sillness & Loe), bleeding index (Cowell) and probing pocket depth (WHO probe). All indices were measured in the 0, 7th and 14th days of the study.

**Results:** Seventy five patients ranged of 15-18 years old were enrolled. At the end of the study, the indices in all groups showed significant decreases in comparison to the first day (p<0.05), except for the bleeding index in the group without SRP and drug therapy (p=0.111). More precise analysis of data revealed that SRP in association with *Frankincense* application (either extract or powder) can lead to remarkable decrease in inflammatory indices in comparison to the groups without SRP and drug therapy (p<0.001). In addition, no significant difference was observed between powder or extract therapy (p>0.05) and between patients received either SRP or treatment alone (p=0.169).

**Conclusion:** *Frankincense*, a safe and low-cost herbal medicine, may be feasibly applied to improve inflammation based disease of gingival as an adjunct to the conventional mechanical therapy.

**Keywords:** Dental plaque, Inflammation, Clinical trial, Herbal medicine.

INTRODUCTION

Gingivitis in its most common form, plaque-induced gingivitis, results from interactions of immune system and existing biofilm. Inflammation as the major pathological manifestation of periodontal diseases is a part of the immune system response to overcome aggregated microorganisms in the plaque. The more severe the response and aggregation of inflammatory cells and mediators, the more the destruction of periodontal tissues. Basically, plaque removal and inflammation reduction are achieved by means of scaling and root planning (SRP) and anti-inflammatory medications, respectively. As daily use of non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase inhibitors (e.g., Celecoxib) can result in complications such as gastrointestinal bleeding, hypertension, congestive heart and renal failures (1), special attention has been recently paid to selective lipooxygenase inhibitors. *Frankincense*, a resin-like extract of *Boswellia* species from Burseraceae family, possessing Boswellic acid (B.A)
is a pentacyclic terpenoid that has been used in the Indian Ayurvedic traditional medicine (ayur: life, veda: knowledge) for many years (2). It has been demonstrated that Acetyl Keto Boswellic Acid (AKBA), as the most active component of boswellia extract, is a selective non-oxidative inhibitor of 5-lipoxygenase pathway (3). This pathway is the key pathway of leukotriens production from arachidonic acid in the cellular inflammatory cascade. Besides, the role of boswellic acid and Frankincense extract has been assessed in inflammatory diseases (4). Other herbal medication such as German Chamomile mouth wash has been reported to reduce dental plaque and gingival inflammation (5). Absence of acute or chronic adverse effects of Frankincense in animals and humans has been guaranteed the low risk of daily use of this medication (6). Taking into consideration the anti-inflammatory and antibacterial effects, low-cost, availability of Frankincense and also relatively high frequency of gingivitis, this study was designed to assess the effect of Frankincense powder or extract in the treatment of gingivitis.

MATERIAL AND METHODS

Study design and eligibility criteria
A randomized, double-blinded (patient, clinician, biostatician), placebo controlled; parallel assigned trial was conducted to determine the safety and efficacy of Frankincense derivatives for treatment of plaque induced gingivitis among female high school students. The students with systemic diseases such as diabetes mellitus, hypertension and gastrointestinal diseases and also those who had used antibiotics or any other periodontal affecting drugs during the previous month were excluded from the study. Besides students with severe malocclusion teeth crowding, prior periodontal surgery and scaling and root planning (SRP) during the last 6 months along with profound Ramfjord teeth decay or filling were excluded from the study. The patient parents or guardians were asked to write informed consent.

Group assignment & Medicaments preparation
Six groups were designed as follows: group 1 (only extract), group 2 (only powder), group 3 (no medicament, no SRP), group 4 (extract and SRP), group 5 (powder and SRP) and group 6 (only SRP). Extracts and powders were prepared from an Indian species, Boswellia Serrata. The placebo (sugar free gum which does not contain any medicament) with the same shape and colour and amount prepared by the same pharmacist who was also responsible for preparation of drugs for entire study. Extract and powder were prepared from an Indian species, Boswellia Serrata. samples were purchased from registered local herbal medicines market. The physical and botanical characteristics of Frankincense were identified and authenticated by an expert specialist in herbal section of Department of Pharmacology, Faculty of Medicine, Babol University of Medical Science, Babol, Iran and a voucher specimen (No: CS_00235) was deposited. Extraction was carried out on fine powder by maceration in 95% ethanol for 48hrs. After filtration, the filtrate was concentrated in rotary evaporator apparatus and then it was added into gum base to make 0.1% w/w preparation. Powder was prepared by the same process as for the extract and was available as gum containing 0.2% w/w. Gum base was obtained from commercially available sugar-free samples from the market.

Study protocol
After informed consent and final enrolment, the participants were subjected to receive either 0.1 g of the extract or 0.2 g powder (in the form of chewing gums) or placebo (pure chewing gums) with or without scaling. SRP was performed at the beginning of the study and participants were instructed to chew three times per day, a gum each time, for 14 days. All groups were also provided with Oral Hygiene instruction (OHI) and safety issues to report any allergy and sensitivity, itching and burning, severe bleeding, ulcer formation or any adverse effects possibly caused by the prescribed medicaments.

Primary and secondary end points
All indices including Gingival Index (GI), Plaque Index (PI), Bleeding Index (BI) and Pocket Probe Depth (PPD) were recorded at the beginning of the study. The primary efficacy outcome was changes in GI (7) and the secondary outcomes were alteration in PI (8), BI (9) and PPD (WHO probe) and other side effects. All indices were measured in the 0, 7th and 14th days of the study by the same clinician with the above mentioned indices in a standard light.

Statistical analyses
Alteration of each index within each group and comparison of same index between groups were assessed by means of repeated measure Analysis of Variance (ANOVA) and One-way ANOVA, respectively. In addition mean difference of each index (Mean Diff.) during the study and overall difference computing for all 4 indices (Total diff.) was designated to reveal the group in which higher level of differences (Improvement in inflammatory indices) was achieved. Finally a pooled group (i.e., A [(only drug therapy (combination of groups 1 and 2)], B [without SRP and drug therapy (group 3)], C [SRP and drug therapy (combination of groups 4 and 5)] and D [only SRP: (group 6)] designs were taken into account to investigate putative effect of medicament. Further, a two-tailed α at p value <0.05 was considered statistically significant. This study
reviewed and approved by the ethical committee of Babol University of Medical Sciences and all investigations were undertaken according to Helsinki treaty.

RESULTS

Study population
Patient recruitment accomplished among female high school students at Babol discrete, Mazandaran province, Iran during 2004-2006. Among 465 students which were assessed for enrolment, 145 had plaque induced gingivitis of which 90 students were included in the study. The most common reason for ineligibility fell into the category of corticosteroids medication followed by systemic disease and option not to participate. Among 90 recruited students, a total of 74 (82%) patients which were randomly assigned to group 1 (only extract, n=15), group 2 (only powder, n=14), group 3 (no medicament and no SRP, n=15), group 4 (extract and SRP, n=10), group 5 (powder and SRP, n=10) and group 6 (only SRP, n=10) completed the study and included in the final analysis.

Baseline characteristics
Characteristics of baseline indices of the patients are listed in table 1 in the day of 0 column for each variable and group. Regarding the comparison of baseline characteristics between groups of the study, a significant difference was observed for all 4 indices, therefore a day by day comparison of groups was overlooked and Mean and Total Diff. were used in calculation.

Primary and secondary end points: Within group analysis
Tracing fluctuation of indices within each group and inter group comparison clarified that at the end of the study, there were improvement in all indices in comparison to the day 0 of the study (p<0.001), except for bleeding index in group 6 (no SRP and medicaments, p=0.111) (Table 1).

Primary and secondary end points: Between group analysis
Differences of changes of indices in the 6 groups were statistically significant (p<0.001), when inter groups were compared. For comparison of effects of extract and powder, comparisons were made between groups 1, 2 and 4, 5. There was no differences between type of medicaments [Post Hoc Bonferroni (group 4 vs.5, p=0.92), (groups 1 vs. 2, p=1)]. Also, it was clear that drugs (extract or powder) had a positive effect in the improvement of indices [Post Hoc Bonferroni (group 1 vs. 3, p=0.008) (group 2 vs. 3, p=0.048), (group 3 vs. 4, p=0.001), (group 3 vs. 5, p=0.002)]. It was figured out that SRP has no significant difference in comparison to groups without SRP, with or without medicaments administration [Post Hoc Bonferroni (group 3 vs. 6, p=1), (group 2 vs. 5 p=1), (group 1 vs. 4, p=0.064)]. A comparison between medicaments effects and SRP, showed that there was no significant difference in overall improvement of indices [Post Hoc Bonferroni (group 1 vs.6, p=0.619), (group 2 vs. 6, p=1)] (Table 1). When Total Diff. was considered, groups showed statistically different effects in overall indices improvement [F (5, 68) =9.32, p<0.001] while group 4 was superior [3.63±1.15] followed by group 5 [2.85±1.13], [2.50±0.96], [2.35±0.97], [1.75±0.76] and 3 [1.32±0.96] (Table 1). Effects of size calculated for GI, PPD and PI were 0.98.

Primary and secondary end points: Pooled group analysis
Significant inter group differences were observed after analysis of pooled data from combined groups considering all indices [F (3, 51.68) =16.01, p<0.001]. Collectively, group C showed better outcomes when calculating the overall improvement in all 4 indices [3.24±1.18], followed by group A, D and B (Table 2). To assess the effect of medicaments or SRP on periodontium health status alone or together, further analyses were carried out. Medicaments with or without SRP were effective [Post Hoc Dunnett T3 (group A vs. B, p <0.001), (group C vs. D, p=0.002)], although SRP itself, had no remarkable effect [Post Hoc Dunnett T3 (group B vs. D, p=0.516), (group A vs. C, p=0.096). Sole treatment with either SRP or medicament had the same impact [Post Hoc Dunnett T3 (group A vs. D), p=0.169], meanwhile combination of SRP and medicament possessed a higher potency to promote periodontal health and to lessen inflammation [Post Hoc Dunnett T3 (group B vs. C, p<0.001)]. Sum of all indices was calculated at the days of 0, 7 and 14. Changing pattern of all pooled indices of comparisons between quadric pooled groups is displayed in figure 1.

DISCUSSION
In this study, anti-inflammatory effects of the extract and powder of Frankincense in the treatment of plaque-induced gingivitis was investigated. Improvement of inflammation of periodontium by the use of extract or powder of Frankincense was remarkable. These findings are in accordance with results of previous investigations upon anti-inflammatory properties of Frankincense (4).
Relative superiority of extract to powder which was not significant may be explained by higher concentration of active components in the resin extract of Frankincense when compared to the powder preparation. In both assessment of 6 and combined 4 groups, the most improvement was found in groups with medicament. Nevertheless, this superiority in medicament treated groups
Table 1. Changing Trends of Periodontal Indices in Various Groups managed with or without *Frankincense* during the Study.

| Index          | Group | Day of 0 Mean (SD) | Day of 7 Mean (SD) | Day of 14 Mean (SD) | Significance | Mean Diff. Mean (SD) |
|----------------|-------|--------------------|--------------------|--------------------|--------------|---------------------|
|                |       |                    |                    |                    | F(1.13,18.38)=58.22, p<0.001 | 0.73(0.32) |
| Gingival Index | 1     | 1.51(0.23)         | 1.02(0.23)         | 0.78(1.23)         |              |                     |
|                | 2     | 1.53(0.30)         | 1.13(0.30)         | 0.88(0.27)         | F(2.26)=75.66, p<0.001 | 0.64(0.20) |
|                | 3     | 1.40(0.19)         | 1.21(0.21)         | 1.10(0.19)         | F(2.28)=65.95, p<0.001 | 0.30(0.09) |
|                | 4     | 1.47(0.43)         | 0.87(0.28)         | 0.60(0.29)         | F(1.14,10.32)=27.34, p<0.001 | 0.87(0.46) |
|                | 5     | 1.16(0.27)         | 0.72(0.18)         | 0.48(0.15)         | F(1.16,10.49)=83.15, p<0.001 | 0.67(0.21) |
|                | 6     | 1.35(0.16)         | 1.12(0.14)         | 0.93(0.16)         | F(2.18)=50.98, p<0.001 | 0.41(0.14) |
| Bleeding Index | 1     | 1.53(0.41)         | 0.77(0.33)         | 0.52(0.33)         | F(1.13,18.38)=75.78, p<0.001 | 0.82(0.33) |
|                | 2     | 1.36(0.50)         | 0.90(0.43)         | 0.65(0.42)         | F(2.26)=54.01, p<0.001 | 0.70(0.30) |
|                | 3     | 1.14(0.38)         | 0.87(0.41)         | 0.73(0.41)         | F(2.28)=54.40, p<0.001 | 0.40(0.16) |
| Plaque Index   | 4     | 1.10(0.56)         | 0.42(0.24)         | 0.19(0.21)         | F(2.27,11.47)=38.18, p<0.001 | 0.43(0.13) |
|                | 5     | 0.70(0.32)         | 0.17(0.10)         | 0.06(0.04)         | F(1.15,10.37)=38.18, p<0.001 | 0.30(0.09) |
|                | 6     | 0.76(0.32)         | 0.58(0.37)         | 0.45(0.37)         | F(1.09,9.81)=3.03, p<0.001 | 0.48(0.15) |
|                |       |                    |                    |                    | F(5,29.05)=7.37, p<0.001 |                     |

Significance: †† p=0.025

| Index          | Group | Day of 0 Mean (SD) | Day of 7 Mean (SD) | Day of 14 Mean (SD) | Significance | Mean Diff. Mean (SD) |
|----------------|-------|--------------------|--------------------|--------------------|--------------|---------------------|
|                |       |                    |                    |                    | F(1.12,14.57)=27.99, p<0.001 | 0.47(0.29) |
| Plaque Index   | 1     | 1.14(0.41)         | 1.06(0.45)         | 0.93(0.34)         |              |                     |
|                | 2     | 1.46(0.54)         | 1.05(0.42)         | 1.01(0.42)         | F(1.12,14.57)=11.01, p<0.001 | 0.44(0.43) |
|                | 3     | 1.23(0.42)         | 0.95(0.38)         | 0.91(0.93)         | F(2.28)=13.90, p<0.001 | 0.32(0.29) |
|                | 4     | 1.84(0.59)         | 0.56(0.27)         | 0.42(0.21)         | F(1.16,10.47)=43.61, p<0.001 | 1.42(0.62) |
|                | 5     | 1.70(0.50)         | 0.64(0.28)         | 0.43(0.26)         | F(1.12,10.10)=40.51, p<0.001 | 0.74(0.46) |
|                | 6     | 1.36(0.49)         | 0.65(0.35)         | 0.62(0.35)         | F(1.12)=0, p<0.001 | 0.70(0.59) |
|                |       |                    |                    |                    | F(5,42.136)=10.70, p<0.001 |                     |

Significance: †† p=0.001
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Table 1. (Continue)

| Index | Group\(^{a}\) | Day of 0 Mean (SD) | Day of 7 Mean (SD) | Day of 14 Mean (SD) | Significance\(^{b}\) | Mean Diff. Mean (SD)* |
|-------|--------------|-------------------|-------------------|-------------------|---------------------|----------------------|
| 1 | 1.71(0.50) | 1.48(0.41) | 1.21(0.27) | F(2,28)=23.41 \(p<0.001\) | 2.53(0.96) |
| 2 | 1.89(0.46) | 1.62(0.34) | 1.33(0.28) | F(2,26)=30.36 \(p<0.001\) | 2.35(0.97) |
| 3 | 1.76(0.42) | 1.63(0.35) | 1.74(0.31) | F(1,41,19.87)=13.64 \(p<0.001\) | 1.32(0.42) |
| 4 | 1.61(0.44) | 1.30(0.30) | 1.18(0.30) | F(1,07,9.68)=34.83 \(p<0.001\) | 3.23(1.15) |
| 5 | 1.32(0.24) | 1.12(0.15) | 1.06(0.13) | F(1,14,10.02)=22.80 \(p<0.001\) | 1.75(0.76) |
| 6 | 1.53(0.37) | 1.34(0.17) | 1.24(0.35) | F(1,13,10.23)=13.81 \(p<0.001\) | 2.34(1.14) |

Significance\(^{\dagger\dagger}\) \(p=0.041\)

\(p<0.001\)

\(F(5,68)=9.32\)

\(p=0.001\)

\(^a\) Group definition: group 1 (only extract), group 2 (only powder), group 3 (no medicament, no SRP), group 4 (extract and SRP), group 5 (powder with SRP) and group 6 (only SRP).\(^{\dagger}\) Within group analysis total change-trend by repeated measurement ANOVA test (Time effect).\(^{\dagger\dagger}\) Between groups’ comparison of total change-trend by One-way ANOVA test.\(^*\) Mean Diff. calculated for average days of 0-14 changes. Day by day comparison was not allowed as groups differed significantly at the day of 0 (\(p<0.05\)). SD: standard deviation.

Table 2. Changing Trends of Indices in Pooled Groups during the Study.

| Group\(^{b}\) | Gingival Index Mean Diff (SD) | Bleeding Index Mean Diff (SD) | Plaque Index Mean Diff (SD) | Pocket Probe Depth Mean Diff (SD) | Total Diff\(^{\dagger}\) (SD) |
|-----------------|-------------------------------|-----------------------------|-----------------------------|----------------------------------|-----------------------------|
| A | 0.69(0.27) | 0.76(0.32) | 0.45(0.36) | 0.53(0.32) | 2.44(0.95) |
| B | 0.30(0.09) | 0.40(0.16) | 0.32(0.29) | 0.28(0.25) | 1.32(0.42) |
| C | 0.77(0.36) | 0.78(0.39) | 1.34(0.61) | 0.34(0.20) | 3.24(0.118) |
| D | 0.41(0.14) | 0.30(0.48) | 0.74(0.46) | 0.29(0.23) | 1.75(0.76) |

Significance\(^{\dagger\dagger}\) \(F(3, 46)=14.68, p=0.001\) \(F(2, 70)=7.95, p=0.001\) \(F(3, 44.59)=20.01, p=0.001\) \(F(2, 58.53)=4.41, p=0.007\) \(F(3, 51.68)=9.32, p=0.001\)

\(^{b}\) Group definition: A [only drug therapy (combination of groups 1 and 2)], B [without SRP and drug therapy (group 3)], C [SRP and drug therapy (combination of groups 4 and 5) and D [only SRP (group 6)].\(^{\dagger}\) Total Diff: Average differences compared for all 4 indices, \(^{\dagger\dagger}\) Between groups’ comparison of change-trend by One-way ANOVA for mean differences calculated for day 0-14 changes, SD: standard deviation.

was hampered in sole SRP groups, although, this difference was not statistically significant (\(p<0.05\)). In addition, in groups which were subjected to medicament therapy or SRP, significant difference was observed in comparison to groups without either medicament or SRP. Also, other than the bleeding index in group which received neither medicament nor SRP (group 6), there were improvements of all indices in all groups, at the end of the study, compared to the first day of the study. It seems that excessive inflammatory reactions due to the mechanical SRP traumatic forces may proceed to obscure the remedial effect of pure chewing gums. It is probable that, by increasing the follow up period up to one month and more, useful effects of mechanical deletion of plaque may become more evident. It should be mentioned that low sample sizes of the studied groups may under- or overestimated the reported outcomes. A 30 percent lost-to-follow up rate in some groups is better to be considered as another limitation and reporting bias of the present work. Previously Jing et al highlighted that Boswellia may exert its effects in a dose and time dependent manner (10). Besides, one should consider that change in patterns may have gradual fashion continued 1-3 months after phase I therapy (11). Improvements in other indices (PI, GI, and PPD) in group 6 probably is related to effects of improved regional blood flow (12) and mechanical ablation of plaque perceived by chewing (13). Cochrane authentic review in 2008 has challenged the anti inflammatory capability of B.A (14). Failure
of AKBA to suppress inflammation in chronic setting may be due to overproduction of peroxidase during oxidative stresses in oxi-redox interactions. In the work described, chewing gum which contained neither powder nor extract of *Frankincense* was used as placebo in the control group. Considering previous reports on the local effect of the gum on gingivitis with probable augmentation of the microcirculation (12), concern may be raised upon biased conclusion about independent anti-inflammatory effect of *Frankincense*.

**CONCLUSION**

Result of this investigation displayed anti-inflammatory properties of *Frankincense* extract on chronic plaque induced gingivitis. This herbal medicament may be feasibly and safely applied to improve gingival health. This naturaceutical exhibits satisfactory remedial properties, which is comparable and even superior to scaling and root planning (SRP) as the current standard of dental plaque removal which are costly and discomfort during the procedure.

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