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The Effectiveness of Propolis on Gingivitis: A Randomized Controlled Trial

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Abstract

Background: A randomized, double-blind, controlled clinical trial was conducted to evaluate the effectiveness of a propolis rinse on induced gingivitis by using the co-twin study design.
Methods: Twenty-one twin pairs ($n=42$) were enrolled in a gingivitis study with oral hygiene promotion (14 days) and gingivitis induction (21 days). During the gingivitis induction phase, one member of the twin pair was randomly assigned to a 2% typified propolis rinse, and the other was assigned a color-matched 0.05% sodium fluoride plus 0.05% cetylpyridinium chloride rinse (positive control). Patients rinsed twice daily with 20 mL for 30 seconds for 21 days. Gingivitis was measured on days −14 (baseline), 0 (after hygiene phase), and 21 (after no-hygiene phase) by using the Papillary Bleeding Score (PBS) and by standard digital imaging of the gum tissues (G-parameter).
Results: The 38 persons who completed the study (age 13–22 years) were well balanced according to PBS at baseline and G-parameter after the initial hygiene phase. After 21 days without oral hygiene, the propolis rinse and positive control rinse groups did not differ significantly for average PBS measurements or G-parameter.
Conclusions: Use of a 2% typified propolis rinse was equivalent to a positive control rinse during a 21-day no-hygiene period.

Introduction

The high prevalence of gingivitis in a representative sample of U.S. adults (range, 56%–94%)[1] highlights the fact that current preventive strategies have not been effective on gingivitis from a population standpoint. Therefore, renewed efforts for the development of new preventive strategies are necessary.

Propolis is a resinous matter collected by honeybees from different plant exudates that is used to seal beehives. Propolis possesses distinct biological activities, such as antibacterial, antiviral, fungicidal, anti-inflammatory, antitumor, and wound-healing properties.[2–4] At least 200 compounds have been identified in different propolis samples of different botanical geographic origins, which may include fatty and phenolic acids and esters, substituted phenolic esters, flavonoids, terpenes, β-steroids, aromatic aldehydes, alcohols, sesquiterpenes, naphthalene, and stilbene derivatives.[4–7]

Propolis use dates back to about 300 BCE, when it was first used for cosmetics and as a therapeutic medicine.[4] Accordingly, propolis has been used in folk medicine since ancient times and is now widely used empirically worldwide. The literature on propolis use and its many attributes in dentistry is extensive. In the oropharyngeal domain, numerous laboratory and clinical reports describe use of propolis against cariogenic organisms,[8] periodontal organisms,[9] respiratory infections,[10] gingival inflammation,[11] endodontic pathogens,[12] and oral ulcers,[13] among other oral conditions. These reports, however, lack evidence on the effectiveness of propolis because adequately designed randomized controlled trials have yet to be conducted. Conversely, double-blind, randomized, controlled design trials have shown that mouthwashes containing sodium fluoride (NaF) plus cetylpyridinium chloride (CPF) controlled supragingival plaque accumulation.[14]

The experimental (i.e., induced) gingivitis model has been used extensively to evaluate the potential clinical efficacy of both dentifrices and mouth rinses containing antimicrobial agents to assess treatment responses.[15–19]

The aim of this study was to assess the effectiveness of a 2% typified propolis rinse on induced gingivitis in a

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single-center, double-blind, randomized, parallel clinical trial.

Materials and Methods

Inclusion/exclusion criteria

Inclusion criteria were (1) age least 13 years; (2) provision of written informed consent; (3) presence of all 12 anterior teeth without caries lesions or restorations; and (4) general good health. Exclusion criteria were (1) severe periodontal disease, as characterized by purulent exudates, generalized mobility, and/or severe recession; (2) any condition that requires antibiotic premedication for the administration of a dental prophylaxis; (3) self-reported pregnancy, intent to become pregnant during the study, or breast-feeding; (4) atypical discoloration or pigmentation in the gingival tissue; (5) fixed orthodontic appliances; (6) any diseases or conditions that could be expected to interfere with safe completion of the study; and (*7*) history of antibiotic use in the previous 3 months.

Study design/demographic characteristics

This study compared a 2% typified propolis rinse with an NaF plus CPC rinse (positive control). Thirty twin pairs were initially screened for eligibility criteria. Nine twin pairs were ineligible because of anterior carious lesions (four twin pairs) and the use of fixed orthodontic appliances (five twins pairs). Twenty-one eligible twin pairs 13–22 years of age signed consent forms and were enrolled into the study.

Nineteen evaluable twin pairs completed the study protocols. Two twin pairs were withdrawn from the study because one twin member did not adhere to study protocols. Recruitment and follow-up visits took place between March and August 2008. Table 1 depicts age, sex, and zygosity before commencement of the trial, which were well balanced between study groups.

After a run-in brushing period (hygiene phase), participants were asked to abstain from tooth brushing and flossing (induced gingivitis) while undergoing twice-daily assigned rinsing. Safety and effectiveness were evaluated weekly over 3 weeks during gingivitis induction, which was followed by prophylaxis to regain relative gingival health. The institutional ethics board independently reviewed and approved the research protocol.

Allocation concealment

We used a computer-generated list of random numbers to allocate groups. Rinses were prepared in dark bottles, which were consecutively numbered according to the randomization schedule. Twins were randomly assigned to one of the two test color-matched rinses. The study coordinator, examiners, and participants were unaware of group allocation. The group identity was generated and maintained in the United States, and the study was conducted in Brazil.

Study protocol

Oral hygiene phase (day −14 to day 0). The medical history of participants was obtained and an oral soft tissue examination was performed, followed by assessment of gingival status according to the Papillary Bleeding Score (PBS)[20] and color digital imaging of the gums. After receiving dental prophylaxis, participants were instructed to return to the site once a day. At that time they brushed under supervision using a battery-powered toothbrush for 2 minutes with a marketed anticavity dentifrice. The second brushing for the day was performed without supervision. This brushing regimen was followed for the next 14 days. Day 0 is the conclusion of the oral hygiene phase and the baseline visit for the induced-gingivitis phase.

Induced-gingivitis phase (day 0–day 21). During this phase, participants were instructed to abstain from all forms of oral hygiene except the administered mouth rinse. Participants returned to the study site once a day (after a meal), at which time they rinsed (with 25 mL for 30 seconds) under supervision with their assigned product. A second rinse was performed at home without supervision before sleep. This rinsing regimen was followed for the next 21 days and digital images of anterior teeth and a PBS exam were performed.

Recovery phase (also day 21 of experimental gingivitis phase). Following the clinical examinations made on day 21 of the induced-gingivitis phase, participants were provided

Table 1. Demographic Characteristics of Study Groups

Demographic/statistic or category	*Propolis* (n = *19*)	*Positive control* (n = *19*)	*Overall* (n = *38*)	*Two-sided* p-*value*
Age (yr)				
Mean (SD)	16.1 (2.59)	16.1 (2.59)	16.1 (2.56)	1.000[a]
Minimum, median, maximum	13, 15, 22	13, 15, 22	13, 15, 22	
Sex, *n* (%)				
Female	11 (58)	11 (58)	22 (58)	1.000[b]
Male	8 (42)	8 (42)	16 (42)	
Zygosity, *n* (%)				
Dizygotic	12 (63)	12 (63)	24 (63)	1.000[b]
Monozygotic	7 (37)	7 (37)	14 (37)	

[a]Two-sided analysis of variance *p*-value for the treatment comparison.
[b]Two-sided chi-square *p*-value for the treatment comparison.
SD, standard deviation.

Table 2. Digital Imaging Gum Color (Redness [G]) for Experimental Groups During the Study Periods

Treatment	*Participants (*n*)*	*Mean (SD)*	*Median*	*Minimum–maximum*
Day −14				
Propolis	19	91.2 (18.74)	97.4	54.1–113.1
Positive control	19	95.4 (12.94)	98.4	59.2–111.3
Day 0				
Propolis	19	95.0 (17.87)	99.3	59.2–117.7
Positive control	19	96.8 (12.61)	99.0	59.7–110.9
Day 21				
Propolis	19	91.2 (16.60)	94.2	57.3–115.6
Positive control	19	94.9 (14.05)	93.8	56.0–115.9

SD, standard deviation.

additional prophylaxis and were monitored thereafter until deemed healthy.

Gingival parameters/primary outcomes

Red-green-blue digital imaging. This system consists of an S2 Pro CCD high-resolution digital color camera (Fuji, Minato, Japan) equipped with a Nikon Micro Nikkor lens (Nikon, Tokyo, Japan) with a linear polarizer to permit cross-polarized light. Gingivitis image analysis used anterior facial images collected with cheek retractors and standardized digital photography and lighting. Red-green-blue values were assessed on the marginal gingiva by using image analysis software, with change in G parameter (redness) as the primary response parameter. Paired images were compared to assess longitudinal responses. This noninvasive objective imaging system provides information that is highly correlated with gingivitis clinical measurements.[21]

Papillary Bleeding Score. After imagery, PBS measurements were made on the mesial buccal surfaces of all teeth, excluding the third molars. To obtain this index, a triangle-shaped toothpick (Stim-U-Dent, Johnson & Johnson, New Brunswick, New Jersey) made of soft, pliable wood is used to stimulate the interproximal papilla. The test was performed by doing one quadrant at a time. The Stim-U-Dent device is inserted horizontally between the teeth from the facial surface, depressing the interproximal papilla by up to 2 mm. It was inserted once, and then the site was scored after 15 seconds. PBS values ranged from 0 (healthy gingiva) to 5 (severe inflammation, marked redness and edema, and tendency to spontaneous bleeding). The PBS has been reported to be the most reproducible and reliable index (both within and between examiners) for measuring the gingival status of patients compared with established indices for gingivitis.[22] PBS was measured by an experienced examiner (ALM). Intra-examiner reliability exercises revealed a κtest score of 0.85, indicating adequate reproducibility of PBS measurements.

Safety/adverse reactions

Oral soft tissues were assessed by visual examination of the oral cavity. The structures examined include the gingiva (free and attached), hard and soft palate, oropharynx/uvula, buccal mucosa, tongue, floor of the mouth, labial mucosa, mucobuccal/mucolabial folds, lips, and perioral area. In addition, any reported adverse reaction to study protocols was documented.

Rinse formulation

Propolis 2% rinse was manufactured at the laboratories of the Department of Pharmacology at Federal University of Santa Catarina, Florianópolis, SC, Brazil. The formulation included 2% typified propolis, mint flavor, polioxyethelers, sorbitol, blue coloring, and water. Propolis rinse was made by using green propolis (State of Minas Gerais, Brazil) evaluated by high-performance liquid chromatography analysis, showing high levels of the phenolic compounds (in

Table 3. Average Whole-Mouth Papillary Bleeding Scores for Experimental Groups During the Study Periods

Treatment	*Participants (*n*)*	*Mean (SD)*	*Median*	*Minimum–maximum*
Day −14				
Propolis	19	0.58 (0.415)	0.5	0.00–1.70
Positive control	19	0.48 (0.379)	0.4	0.00–1.31
Day 0				
Propolis	19	0.29 (0.320)	0.2	0.00–1.12
Positive control	19	0.37 (0.437)	0.2	0.00–1.73
Day 21				
Propolis	19	0.51 (0.485)	0.3	0.00–1.42
Positive control	19	0.48 (0.396)	0.3	0.00–1.42

SD, standard deviation.

Table 4. Change from Baseline Digital Imaging Gum Color Redness (G)

Treatment	*Participants (*n*)*	*Baseline mean*	p-*Value*[a]	*Mean (SD)*	p-*Value*[b]	*Median*	*Minimum—maximum*
Day 0							
Propolis	19	91.2	0.206	3.8 (4.72)	0.003	5.1	−4.1 to 11.5
Positive control	19	95.4		1.3 (5.16)	0.270	1.5	−12.6 to 8.5
Day 21							
Propolis	19	94.2	0.576	−3.0 (3.84)	0.004	−3.2	−9.5 to 4.8
Positive control	19	96.0		−1.1 (5.21)	0.384	−0.3	−11.9 to 7.1

[a]Two-sided *p*-value for the baseline treatment comparison.
[b]Two-sided paired-difference *p*-value.
SD, standard deviation.

mg/g): coumaric acid (3.81), rutin (9.87), pinobanksin (3.48), quercetin (2.15), kaempferol (0.78), apigenin (1.86), pinocembrin (22.55), pinobanksin-3-acetate (4.10), chrysin (2.49), galangin (4.14), kaempferide (5.59), tectochrysin (2.90), and artepillin C (87.97). The content of phenolic compounds was 151.69 mg of dried extract per g. The formulation of the positive control rinse (Reach, Johnson & Johnson, São José dos Campos, SP, Brazil) contains 0.05% NaF, 0.05% CPC, blue coloring, alcohol, and sucralose.

Statistical analysis

The co-twin study design exploits matching on many observed and unobserved factors and hence provides extremely attractive sampling units for test-control studies.[23,24] This fact forms the basis for the often-used ''co-twin'' designs in epidemiology.[25,26] The stronger the residual phenotypic correlation between the twins (i.e., the phenotypic correlation between the twins that is attributable to known factors), the greater the power to detect differences (e.g., via a *t*-test) in the twins' phenotypic values, in this case gingival inflammation outcomes. Hence, by using the co-twin study design, reduced sample sizes can provide information that would otherwise require larger cohorts.

The average color of gingival tissue within 1.5 mm of the gingival margin of the anterior dentition (facial surfaces) was calculated for each participant at day −14, day 0, and day 21 by digital imaging. A whole-mouth average PBS was calculated for each participant accordingly. Analysis of covariance was used to allow for comparisons between study groups with respect to average gingival redness (G parameter) and bleeding (PBS). A separate statistical model was used to test each hypothesis at each visit. The baseline value of each respective endpoint was used as the covariate in each model. A general linear mixed model was used to compare G and PBS at day 21 between rinse groups, with day −14, day 0, zygosity, and age used as fixed effects and family ID as a random effect. Data were analyzed with the SAS/STAT software (Cary, North Carolina).

Results

The aim of this study was to assess the effectiveness of a 2% typified propolis rinse on induced gingivitis in a single-center, double-blind, randomized, parallel clinical trial.

With the exception of one participant who reported staining of the teeth in the propolis group, no adverse reactions related to study procedures occurred. Tables 2 and 3 provide results for average whole-mouth PBS values and average digital imaging gum color (G parameter) for the hygiene phase and for the induced-gingivitis period. Groups were well balanced at the beginning of the hygiene phase (day −14) and remained so for the start of the induced-gingivitis phase (day 0). Duration of the induced-gingivitis phase (gingival inflammation measured by digital imaging) and average whole-mouth PBS did not significantly differ between groups.

In Tables 4 and 5, footnote ''a'' refers to *p*-values from analysis of variance comparing group means at days 0 and 21, which show that there are no significant differences between groups for either gingival parameter. Footnote ''b'' refers to paired *t*-tests for comparing the mean change from baseline to zero (to see whether the incremental change was statistically significant within each treatment group). For Tables 4 and 5, ''baseline'' refers to day −14 for the day 0 visit and day 0 for the day 21 visit. For the G-parameter (Table 4), no significant changes from baseline were observed for the positive control group at days 0 and 21. The propolis group had significant contrasting outcomes for the G-parameter from baseline at

Table 5. Change from Baseline for Whole-Mouth Papillary Bleeding Score

Treatment	*Participants (*n*)*	*Baseline mean*	p-*Value*[a]	*Mean (SD)*	p-*Value*[b]	*Median*	*Minimum—maximum*
Day 0							
Propolis	19	0.6	0.364	−0.28 (0.425)	0.009	−0.2	−1.52 to 0.27
Positive control	19	0.5		−0.11 (0.363)	0.206	−0.1	−0.92 to 0.42
Day 21							
Propolis	19	0.3	0.542	0.20 (0.404)	0.052	0.1	−0.65 to 1.00
Positive control	19	0.4		0.09 (0.380)	0.345	0.1	−0.96 to 0.85

[a]Two-sided *p*-value for the baseline treatment comparison.
[b]Two-sided paired-difference *p*-value.
SD, standard deviation.

Table 6. Treatment Comparisons: Analysis of Covariance for Digital Imaging Gum Color (Redness [G]) and Papillary Bleeding Scores

		Treatment Comparisons				Variances	
Treatment	*Adjusted mean (SEM)*	*Versus*	*Estimate (SEM)*	*95% Confidence interval*	*Two-Sided* p-*value*	*Error*	*Between-family*
Day 21 PBS							
Propolis	0.50 (0.08)	Positive control	−0.54 (1.52)	−3.75 to 2.67	0.7276	12.442	17.757
Positive control	0.50 (0.08)						
Day 21 gum color (G)							
Propolis	91.75 (1.11)	Positive control	−0.00 (0.11)	−0.23 to 0.23	0.9901	0.000	0.106
Positive control	93.29 (1.17)						

SEM, standard error of the mean.

days 0 and 21. Similar results were observed for average PBS measurements (Table 5). Table 6 compares average values for G-parameter and PBS between groups after the induced gingivitis phase (day 21) controlling for visit, zygosity, and age. There were no significant differences between groups for the observed parameters.

Discussion

This clinical trial was designed as an equivalence trial.[27] Equivalence trials are often used to compare a new treatment with a standard therapy, although it is not possible to determine whether two treatments have exactly equivalent effects. In this manner, equivalence trials are designed to show that two treatments produce effects that would be indistinguishable from the perspective of clinical relevance.[28] Equivalence trials are often used to demonstrate that a new product has been developed because of unique or advantageous characteristics, where, for instance, the propolis rinse can be deemed as a naturally occurring oral formulation.

In considering the above premise, it becomes clear that the induced-gingivitis model is suitable for the conduction of equivalence trials. This model permits assessment of the effectiveness of oral rinses on primary outcomes related to gingival inflammation in the absence of routine oral hygiene procedures that are customarily performed by the general population. It is conceivable that a protocol that would not prevent individuals from abstaining from their daily oral hygiene practices would have potentially shown different results.

Our results clearly show that a 2% typified propolis rinse was equivalent to a positive control rinse containing 0.05% NaF and 0.05% CPC when indicators of gingival inflammation were used as primary outcomes in the induced-gingivitis model (Tables 3–6). No clinical trials have assessed the effects of propolis on gingivitis. A recent phase II study on the efficacy of a 5% typified propolis (green propolis) mouthwash clearly demonstrated that twice-daily use of the rinse for 90 days amounted to a 77% reduction in the levels of gingival inflammation when compared with baseline levels.[11]

Because of a striking variability in propolis chemical composition based on botanical origin, it is imperative that methods of standardization (typification) are used to describe the biologically active components present in any formulation that contains propolis. The propolis rinse used in this study contained propolis samples from Minas Gerais, Brazil, that were typified and classified as BRGx[29] with markers that exhibit antimicrobial and anti-inflammatory activity. This is crucial for comparisons between studies of propolis formulations and their corresponding therapeutic activities.

In conclusion, this study has demonstrated that the use of a 2% typified propolis rinse was equivalent to a positive control rinse during a 21-day induced-gingivitis model. Further studies on the effects of propolis on gingivitis should be conducted by other investigators using similar protocols.

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Author Disclosure Statement

No competing financial interests exist.

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