The Effectiveness of Mangosteen Peel (*Garcinia Mangostana L*) Extract Mouthwash on Reducing Gingival Inflammation

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Abstract

Gingival inflammation or gingivitis is an inflammation of the gingiva caused by deposits of supragingival plaque characterized by changes in clinical features. Treatment of gingivitis consists of mechanical procedure through scaling and root planing, but mechanical procedure alone sometimes is not effective, therefore mechanical treatment should be combined with adjunctive therapy. Mangosteen peel is an ingredient that has anti-inflammatory and antibacterial properties. This study aims to determine the effectiveness of mangosteen peel extract mouthwash in reducing gingival inflammation.

This study was conducted using a double-blind simple randomized-controlled trial. A total of 32 subjects with gingivitis were randomly assigned into 4 different groups, namely group I placebo, group II concentration of 2%, group III concentration of 4%, and group IV concentration of 6%. All subjects were given scaling as initial treatment then, the Modified Gingival Index (MGI) and Sulcular Bleeding Index (SBI) score were measured on the 1st and 8th days.

The MGI and SBI scores are reduced in all groups on the 8th day. A significant MGI score reduction was seen in concentration 2% and concentration 6% compared to negative control and no significant differences between the two concentrations

Mangosteen peel extract mouthwash can reduce gingival inflammation with the highest reduction seen at concentrations of 2% and 6% viewed based on the MGI parameter.

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Introduction

Periodontal diseases consist of gingivitis and periodontitis, are common diseases affecting people in Indonesia with a prevalence of 74.1%.[1] Gingivitis is an inflammation on the gingiva marked with clinical conditions such as swelling, redness, alteration of the gingiva's texture, and gingival bleeding.[2] The most common etiology of gingivitis is accumulation of supragingival plaque combined with the interaction between biofilm bacteria and host response.[3,4] Bacterial plaque has the ability to synthesize bacterial products, which causes inflammation and damage on epithelial tissue and gingival connective tissue.[5] Delayed treatments to gingival inflammation may become the primary precursor of periodontitis. A study reported a linear relationship between gingival inflammation and the occurrence of periodontitis, therefore management of gingival inflammation and plaque control procedures are needed to prevent the disease from becoming more severe.[6]

The primary treatment of gingivitis involves mechanical procedures such as scaling and root planing and through maintaining good oral hygiene.[2,7] However, mechanical treatment alone, in some cases, cannot provide adequate results since it only applies to areas reached by periodontal instruments. Meanwhile, inflammation would still occur in unreachable areas, such as deep pockets.[8,9] Currently, many studies recommend combining mechanical and adjuvant treatments to control inflammation so that the result can be more effective.[10] One of the most common adjuvant treatment methods is using mouthwash. One of the advantage of mouthwash is it is available in liquid form hence, the active agents of the mouthwash can be

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distributed to all teeth surfaces.[11]

Mangosteen (*Garcinia mangostana L.*) is one of the natural resources that has been used for a long time as herbal medicine for many types of diseases. Xanthone, one of main content in the mangosteen peel provides excellent antibacterial and anti-inflammation effects.[12] A study by Widowati *et al.*[13] showed that the prenylated xanthone such as α-mangostin dan γ-mangostin have an anti-inflammation ability through inhibition of inflammatory mediators such as COX-2, IL-6, IL-1β, and nitric oxide (NO). According to Nittayananta *et al.*[14] in their study, α-mangostin embodied oral sprays have antibacterial, antibiofilm, and anti-inflammation effects without causing cytotoxic effects therefore, they can be developed as an oral product in the forms of spray, gel, or mouthwash. Another anti-inflammatory agent in mangosteen peel is flavonoid. Flavonoid works by preventing the release of arachidonate acid through inhibition of phospholipase A2 (PLA2), and disrupt the exudation phase of the inflammation process.[15,16]

Previous clinical study by Hendiani *et al.*[17] reported that applying mangosteen peel extract gel as an adjunctive treatment after scaling and root planing could lowered the MMP-8 level in chronic periodontitis patients. The MMP-8 level acts as a biomarker of inflammation in the periodontal tissues. Clinical study by Vinayaka *et al.*[18] reported that mangosteen peel extract gel 4% is an effective supplementary treatment after scaling and root planing and can be an alternative therapeutic agent without any side effects for plaque-induced gingivitis treatment. The mangosteen peel extract also has an antibacterial effect, therefore, it can inhibit the growth of bacterial plaque in the oral cavity that cause plaque-induced gingivitis. An in vitro study by Hendiani *et al.*[19] showed that the ethanol extract of mangosteen peel in concentration of 1.56%, 3.125%, and 6.25% having an inhibitory and bactericidal properties to Prophymonas gingivalis and Actinobacillus actinomucetecomitans.

The anti-inflammatory and antibacterial effects of mangosteen peel extract have been studied in many dosage forms and concentrations. It also said that mangosteen peel extract has the potential to be implemented as a therapeutic agent. To date, there have not been any studies that discuss the anti-inflammatory effects of mangosteen peel extract in the dosage form of mouthwash against gingival inflammation. Hence, this study aimed to compare the effectiveness of the mangosteen peel extract in concentrations of 2%, 4%, and 6% in reducing gingival inflammation.

Materials and methods

The present study is an experimental study using simple randomized-controlled trials (RCT) double-blind. The study population are patients from Periodontology Clinic of Dental and Oral Hospital of Universitas Padjadjaran. The sample size determination was according to Federer's formula and considered the dropout rate of 20% hence, the sample size of this study was 32 patients. This study has acquired an ethical approval from the Research Ethical Committee of Universitas Padjadjaran with the number 189/UN6.KEP/EC/2023.

Inclusion and exclusion criteria

The inclusion criteria of this study were 1) Young adult age group (15-24 years); 2) good general health condition; 3) gingivitis patients with inflammation criteria more than score 1 and less than score 3 based on MGI parameter; 4) presence of permanent anterior mandibular teeth (22, 23, 24, 25, 26, 27). The exclusion criteria of this study were 1) patients with fixed orthodontic or prosthetic appliances; 2) severe crowding; 3) consuming antibiotic in the past three months; 4) patients with systematic disease; 5) pregnant women.

Study instruments

Materials used in the preparation of mouthwash are mangosteen (Garcinia mangostana L) peel extract, sodium saccharin, peppermint oil, sodium benzoate, tween 80, and aquadest. The formulation was based on the study conducted by Nurhadi[20] with a modification according to the Handbook of Pharmaceutical Excipients.[21] Instruments used in the clinical study were WHO dental probes, dental mouth mirrors, and ultrasonic scalers.

Preparations of mangosteen peel extract mouthwash

Four kilograms of mangosteen peel (Garconia mangostana L.) powder was obtained from the Special Region of Yogyakarta, Indonesia. Mangosteen peel was extracted using maceration method with 70% ethanol as a solvent and was macerated for 3×24 hours. The extract products were then tested in

phytochemical screening to discover the flavonoid, tannin, polyphenol, alkaloid, quinone, saponin, and triterpenoid contents. The extraction and phytochemical test were conducted at the Herbal Study Center of Universitas Padjadjaran.

The preparations of the mangosteen peel extract mouthwash was conducted at the Pharmaceutical Technology Laboratory Universitas Padjadjaran. Materials were prepared and weighed according to the prescribed formulation. Tween 80, sodium saccharin, sodium benzoate, and water were combined and stirred using the magnetic stirrer until dissolves; solution 1 was made. Peppermint oil and mangosteen peel extract were mixed; solution 2 was made. Solutions 1 and 2 were integrated using the magnetic stirrer until both were homogenous. The mouthwash was filtered using a paper filter and put into bottles. Each bottle of mouthwash was labeled with particular codes, and the concentration of the codes was noted. Only researcher 2 knew the concentration of each mouthwash bottle. Study subjects and researcher 1, as the main researcher, were unaware of the concentrations.

Study design and research groups

The study design used in this study was simple randomized-controlled trial (RCT) double-blind with pre- and post-study design. Thirty-two study subjects were randomly divided into group I, II, III, and IV using randomizer.org website. The test groups were group I scaling and placebo, group II scaling and 2% mangosteen peel extract mouthwash, group III scaling and 4% mangosteen peel extract mouthwash, and group IV scaling and 6% mangosteen peel extract mouthwash.

The subjects were instructed to gargle 10–20 mL mouthwash for 30 seconds and repeat twice daily. The activity was done routinely for 7 days. Subjects were also instructed to brush their teeth using the same toothbrush and toothpaste, and were given the tooth brushing technique beforehand.

Clinical parameter

This study used Modified Gingival Index (MGI) and the Sulcular Bleeding Index (SBI) as clinical parameters. The clinical assessment was conducted on the 1st and 8th days. Partial mouth method used as the scoring method, which evaluates only the anterior mandibular teeth. Prior to the research, a calibration test using Cohen's Kappa on six subjects was conducted, resulting in a score of 75%.

Statistical Analysis

The data analysis was carried out using the SPSS IBM Application version 25.0 (SPSS Inc., Chicago, Illinois). A normality test using the Shapiro-Wilk Test and a homogenous test were conducted. The gingival index score differences before and after treatment were analyzed using the paired sample t-test if the data was distributed normally or the Wilcoxon test if the data was distributed abnormally. The gingival index score differences between the groups was analyzed using the One-way ANOVA test if the data is distributed normally or the Kruskal-Wallis test if the data is distributed abnormally. The Post Hoc Tukey test followed the One-way ANOVA test if the analysis result is a significant score.

Results

The study was conducted on 32 patients of the Periodontology Clinic at the Dental Hospital of Universitas Padjadjaran based on inclusion and exclusion criteria. During the study, one subject was excluded due to absence; therefore, the final total subject was 31 people (female: 19, male: 12). The age median of the subjects was 22 with age range between 19 – 23 years old

In advance of the preparation of the mouthwash, the mangosteen peel extract was tested using phytochemical screening. The phytochemical test detected flavonoid, polyphenol, quinone, saponin, and triterpenoid as the active contents.

The mouthwash was handed out to the subjects and was used for seven days. The Modified Gingival Index (MGI) and the Sulcular Bleeding Index (SBI) assessments were carried out on the 1st day—before treatment—and the 8th day. The data analysis of the MGI and SBI score before and following the treatment is provided in Table 1. The mean MGI score decreased in the placebo, concentration of 2%, concentration of 4%, and concentration of 6% group after the treatment. The analysis results also showed a significant differences between the MGI score before and after treatment in all test groups (p<0.05). The data analysis on the SBI score also showed a decrease in the SBI score after treatment, similar result to the MGI score. The differences in the SBI score before and after

treatment reported a significant result (p<0.05).

Parameter	Test group	Assessing period	n	Mean	SD	Mean derivation	P-value
MGI	Placebo†	Before (1st day)	7	2.39	0.48	0.64	0.01*
		After (8th day)		1.75	0.54		
	2% Concentration†	Before (1st day)	8	2.46	0.29	1.37	0.000*
		After (8th day)		1.09	0.41		
	4% Concentration†	Before (1st day)	8	2.54	0.25	1.15	0.000*
		After (8th day)		1.38	0.48		
	6% Concentration‡	Before (1st day)	8	2.37	0.33	1.34	0.01*
		After (8th day)		1.03	0.39		
SBI	Placebo†	Before (1st day)	7	0.77	0.17	0.29	0.006*
		After (8th day)		0.48	0.23		
	2% Concentration†	Before (1st day)	8	0.64	0.26	0.30	0.003*
		After (8th day)		0.34	0.14		
	4% Concentration†	Before (1st day)	8	0.63	0.26	0.22	0.01*
		After (8th day)		0.41	0.14		
	6% Concentration†	Before (1st day)	8	0.52	0.17	0.27	0.001*
		After (8th day)		0.25	0.21		

Table 1. Mean differences of MGI and SBI before (1st day) and after (8th day) the treatment.
n: number of subjects; SD: standard deviation; *P-value< 0,05 significant; †Paired t-test, ‡Wilcoxon test.

Parameter	Assessing period	Placebo	2% Concentration	4% Concentration	6% Concentration	P-value
MGI	Before (1st day)†	2.39	2.46	2.54	2.37	0.73
	After (8th day)†	1.75	1.09	1.38	1.03	0.01*
SBI	Before (1st day)†	0.77	0.64	0.63	0.52	0.09
	After (8th day)†	0.48	0.34	0.41	0.25	0.07

Table 2. Comparisons of MGI and SBI mean scores between test groups.
*P-value<0,05 significant, †Anova test.

Table 2 provides the mean comparisons of MGI and SBI parameters in all groups before (1st day) and after (8th day) treatment. There was no significant differences in MGI and SBI scores assessed on the 1st day and SBI scores assessed on the 8th day (p>0.05). However, the MGI scores happened to be significant on the 8th day (p 0.01). The insignificant *p-value* on the 1st day indicated the homogenous subjects in both parameters.

Parameter	Placebo	2% concentration	4% concentration	6% concentration	P-value
MGI†	0.64	1.37	1.15	1.33	0.005*
SBI‡	0.29	0.30	0.22	0.27	0.88

Table 3. Comparison of MGI and SBI mean derivations between test groups.
*P-value<0,05 significant, †Anova test, ‡Kruskal-Wallis test.

Table 3 provides the comparisons of MGI and SBI mean derivation between all test groups. The analysis results of SBI scores showed no significant mean differences in all groups (p 0.88). Meanwhile, the results of MGI scores showed a significant mean differences (p 0.005).

Table 4 comparing the mean derivation of MGI scores between every test groups. A significant result was discovered in the mean derivation between the placebo and the 2% concentration, and the placebo and 6% concentration group. The test results also showed that there was no significant mean derivation between the 2% and 6% concentration groups.

Test groups	Compared to	Mean deviation	P-value
Placebo (Aquades)	2% concentration	-0.72	0.007*
	4% concentration	-0.51	0.07
	6% concentration	-0.69	0.01*
2% concentration	Placebo (Aquades)	0.72	0.007*
	4% concentration	0.21	0.69
	6% concentration	0.03	0.99
4% concentration	Placebo (Aquades)	0.51	0.07
	2% concentration	-0.21	0.69
	6% concentration	-0.18	0.79
2% Concentration	Placebo (Aquades)	0.69	0.01*
	2% concentration	-0.03	0.99
	4% concentration	0.18	0.79

Table 4. The post-hoc Tukey test of MGI mean derivation for all of the test group.
*P-value<0,05 significant.

Discussion

This study aimed to discover the effectiveness of mangosteen peel extract mouthwash in decreasing gingival inflammation in individuals with gingivitis. The effectiveness was assessed through the visual measurement of the gingival index score using the Modified Gingival Index (MGI) and the gingival bleeding index score using the Sulcular Bleeding Index (SBI). This study's results showed a significant change in the MGI and SBI scores following the treatment both in the control group (placebo) and the test groups (2%, 4%, and 6% concentration). The reduction of the gingival index score in all groups occurred due to the reduced gingival inflammation following the scaling procedure. These findings align with the results of studies by Singh *et al.*[22] and Koppolu *et al.*[23] that stated there is a clinical parameter decrease of the gingival index and bleeding on probing in patients with gingivitis after scaling and root planning treatments. Gingivitis is a reversible type of disease and is occurred due to the accumulation of dental plaque and calculus. The initial phase of gingivitis can be hindered its continuance by routinely performing oral hygiene. If gingivitis continues to the next phase and

tissue alteration is visible, the treatment must be conducted professionally through mechanical method of plaque and calculus control, such as scaling and root planning using hand instruments or ultrasonic scaler.[2]

The data analysis resulted in a change in the clinical parameter scores in all groups, but it was discovered that the mean derivation of MGI scores was higher in the test groups compared to the control group. Herbal mouthwash contains abundance of active compounds that could increase the effectiveness of gingivitis treatment. Mahyari et al.[24] in her research proved that a polyherbal mouthwash containing extracts of *Zingiber officinale, Rosmarinus officinalis,* and *Calendula officinalis* was effective in treating gingivitis which characterized by a decrease in the MGI score of the patients. These herbal ingredients have phenolic and flavonoid components which play role as an anti-inflammatory and antibacterial effects. In this study, a higher decrease in the test groups occurred because one of the mangosteen peel extract's properties is an anti-inflammatory, which reduces gingival inflammation after scaling procedure. An *in vivo* study by Putri K *et al.*[15] proved the anti-inflammatory property of the mangosteen peel extract gel in the healing process of gingival inflammation in rats, which was indicated by a significant difference in the size of gingival edema before and following the administration of the gel. Clinical research by Bhanushali et al.[25] stated that mangosteen extract mouthwash has anti-inflammatory and anti-plaque properties because its effectiveness in reducing gingival index score with the same ability as chlorhexidine mouthwash.

Phytochemical test on the mangosteen peel extract in this study showed the extract comprised polyphenol contents. One of the polyphenol contents in the mangosteen peel is xanthone with the most abundant types include are α- and γ-mangostin[25]. Xanthones suppress inflammation process by disrupting the phospholipase pathway through the inhibition of the cyclooxygenase enzyme (COX). COX-1 and COX-2 are essential enzymes in converting arachidonate acid to prostaglandin and inducing other inflammatory mediators. COX inhibition can obstruct the production of prostaglandin and other inflammatory mediators.[13,15] The disruption of the production of prostaglandin and other prostanoid components leads to the inactivation of the *cyclase cyclic adenosine monophosphate* (cAMP) and the *cyclic guanosine monophosphate* (cGMP) in the blood vessel endothelial cells hence, vasodilation of the blood vessel and gingival redness reduce.[12]

Other than the anti-inflammation property, the reduction of gingival inflammation also occurred due to the antibacterial property in the mangosteen peel extract. Previous studies reported that the ethanol extract from mangosteen peel can inhibit the growth of bacteria and is bactericidal towards bacterial plaque such as *Streptococcus sanguinis, Prophymonas gingivalis,* and *Actinobacillus actinomycetemcomitans.*[19,26] The antibacterial property of the mouthwash in this study was attributed to the α-mangostin, flavonoid, quinone, saponin, and triterpenoid contents in the mangosteen peel extract. Xanthone specifically α-mangostin interacts with the bacterial membrane cells to depolarize and induce a leakage in the membrane cell.[27] Flavonoid binds with the bacterial protein and impairs the metabolism process, inhibiting the bacteria's oxygen usage, and the bacterial enzyme biosynthesis will be hampered. Flavonoids can alter the bacterial membrane cells' functions by forming a complex content with the extracellular protein, resulting in bacterial membrane cell damage. Saponin can elevate the membrane cell permeability, resulting in cell hemolysis. Triterpenoid disrupts the components of the bacterial cell wall through its interaction with the lipophilic layer of phospholipid membrane cells, decreasing membrane integrity which leads to cell lysis and cell death.[28,29]

The analysis results of the SBI scores showed insignificant mean derivation both in the test group (mangosteen peel extract mouthwash) and control group (placebo) (p=0.88). Studies by Muhlemann & Son[30] and Meitner *et al.*[31] reported that the gingival areas tested positive in the bleeding on probing were considerable found in greater number than the gingival area with visual alterations. The explanation for this findings is that bleeding on probing is considered the primary indicator of gingivitis occurrence in the initial phase before any visual alterations happen therefore, occasionally, bleeding on probing can be found in the gingival areas with no sign of visual alteration.[2,32] A histopathologist study revealed that the gingival area with bleeding on probing consisted of less connective tissue,

epithelium tissue, and inflamed blood vessels than the gingival area with visual alterations.[33] In addition, the SBI index utilized in this study had a relatively wide scale because the assessment of gingival inflammation only used two categories, which scored zero if bleeding on probing is not detected and scored one if bleeding on probing is detected. The wide scale of the index leads to less precise gingival inflammation assessment results.

Based on the analysis results in Table 3, there was no significant mean differences in MGI and SBI scores assessed on the first day, hence, the gingival index in all subjects on the first day was homogenous. The analysis of the mean derivation of MGI scores in Table 4 showed the 2% and 6% mangosteen peel extract mouthwash had better effectiveness compared with the negative control group and there is no significant score decrease in both groups (p=0.99). These findings were in accordance with a study by Arini *et al.*[32] that proved the usage of mangosteen peel boiled water was effective in treating gingivitis post-dental treatments. However, the 4% mangosteen peel extract was discovered to have a weaker ability to reduce gingival inflammation compared to 2% mouthwash and did not result in a significant reduction of gingival index score compared to the placebo group. These findings contradict a study by Husna *et al.*[33] that reported the 4% mangosteen peel extract gel could reduce the gingival index score significantly compared to the placebo group. This condition might occur due to uncontrollable factors such as patients' obedience to use the mouthwash and follow the instruction, which impacted the study result. Furthermore, this study also had limitations because it was conducted in a short period with relatively few subjects.

To overcome the limitations, the researchers suggest conducting a study with a bigger number of subjects and a longer period and utilizing other type of study design and method that can manage the factors that might influence the objectivity of the study results.

Conclusions

The mangosteen peel extract mouthwash was proven to reduce gingival inflammation. 2% and 6% concentrations of mangosteen peel extract in the mouthwash had an excellent capacity to reduce gingival inflammation based on the reduction in the Modified Gingival Index (MGI) parameter.

Declaration of Interest

The authors report no conflict of interest.

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