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The effect of 4% mangosteen peel extract gel on interleukin-6 (il-6) levels and clinical parameters in stage iii grade b periodontitis patients

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Abstract

Interleukin-6 (IL-6) is a proinflammatory cytokine that is produced locally in inflamed tissues after the activation of lipopolysaccharides and other cytokines such as in patients with periodontitis. Mangosteen peel extract gel application as a form of local application therapy contributed to the reduction of IL-6 and clinical parameters in stage III grade B periodontitis patients. This study aimed to analyze the effect of 4% mangosteen peel extract gel as additional scaling and root planing therapy on IL-6 levels in patients with stage III grade B periodontitis. This study was a pre and posttest control group design study with the number of samples divided into 2 groups. This study used 4% mangosteen peel extract gel which was administered locally into the subgingival after scaling and root planing and placebo gel was used as a comparison. Gingival crevicular fluid was taken before and after treatment in each group and IL-6 levels were measured using the ELISA kit Bioassay. The mean decrease in IL-6 levels before and after subgingival application of 4% mangosteen peel extract gel was significant ($p < 0.05$) i.e. (48.91 ± 19.89) compared to the placebo control group (8.83 ± 12.17). There was a significant difference ($p < 0.05$) in the decrease in clinical parameters in the test group compared to the control group.

Keywords: Mangosteen peel extract, IL-6, periodontitis, cytokines

1. Introduction

Periodontitis is an inflammatory disease involving the alveolar bone, gingiva and supporting connective tissue, affecting the shape of the alveolar bone and the development of periodontal pockets, this condition predisposes to tooth loss. The role of IL-6 in periodontitis has been widely reported in various studies and has shown an association between elevated levels of IL-6 with periodontal tissue destruction. Elimination of microorganisms and inflammation in the periodontal tissues is achieved through mechanical therapy which is considered the main standard procedure with systemic antimicrobials as adjunctive therapy, however these antimicrobials have unwanted side effects including increased resistance due to inappropriate systemic use and hypersensitivity reactions [1, 2, 3]. Local Drug Delivery (LDD) is an important issue in the field of periodontology to have the rate and relative amount of drug in the surrounding tissue without side effects, such as being able to reach the bottom of the periodontal pocket and be maintained for a sufficient amount of time until the antimicrobial effect occurs [5]. Currently, various natural ingredients have been used to assist or accelerate the wound healing process [2]. *Garcinia mangostana* L (mangosteen) which has been shown to have anti-inflammatory and osteogenic effects in the wound healing process and has been applied in dentistry, when topical gels are applied as an adjunct to periodontal treatment was found to increase the clinical effect of periodontal treatment [3, 4]. Mangosteen contains a family of tricyclic isoprenylated polyphenols called xanthenes. The most abundant xanthenes in the mangosteen fruit are α - and γ -mangostin [7]. α -mangostin has also been shown to be a histaminergic and serotonergic receptor blocking agent as well as an inhibitor of several inflammatory mediators such as Nitric Oxide (NO), Prostaglandin E2 (PGE2), induced Nitric Oxide Synthase (iNOS), Cyclooxygenase-2 (COX-2) [8].

This research aimed to analyze the effect of 4% mangosteen peel extract gel subgingival application after scaling and root planning on IL-6 reduction and analyzed the correlation of IL-6 concentration reduction with clinical parameters of stage III grade B periodontitis patients.

2. Materials and Methods

This study use an experimental type of research with pre and post test control group design, namely measuring and observing before and after being given treatment. Determination of the research sample was done by purposive sampling technique. Gingival crevicular fluid samples were taken from periodontitis stage III grade B patients at the Periodontics Installation USU RSGMP who met the inclusion criteria. Ethical clearance approval was obtained from the Research Ethics Commission of Faculty University of North Sumatera and study participants were given an explanation of the procedure from the beginning to the end of the study and signed an informed consent. Inclusion criteria: patients with periodontitis Stage III grade B patients aged from 30 - 65 years, pocket depth ≥ 6 mm, loss of clinical attachment level ≥ 5 mm, the number of teeth in the oral cavity is at least 10 teeth, healthy condition (active and not suffering from systemic disease), exclusion criteria: pregnant and breastfeeding, taking vitamins, antibiotics, and anti-inflammatory for the last 1 month, use mouthwash regularly, patient diagnosed with periodontitis stage IV grade C. This study was divided into 2 group, the test group (4%

Mangosteen peel extract gel) and the control group (placebo gel). Gel applied to one tooth with a pocket depth of 6 mm (in the test group) with the control group placebo gel was applied to one tooth with a pocket depth of 6 mm. The gel is put into the pocket with the help of a blunt-tipped syringe. The gel was inserted up to the gingival margin, waited for 10 minutes and then covered with a periodontal pack. The patient was instructed to maintain his oral hygiene. The patient was asked to come back on day 7, the gingival crevicular fluid was taken again and clinical parameters were measured. Clinical examinations were conducted on 1st and 7th day with clinical examinations of the gingival Index (GI), pockets depth (PD) and clinical attachment loss (CAL) and then Followed by a laboratory procedure using the Enzyme-Linked Immunosorbent Assay (ELISA) methods. Differences in interleukin-6 levels before and after scaling from the control group were first tested for normality using the Shapiro Wilk test. The difference in IL-6 levels before and after in the test and control groups was normally distributed, so it was analyzed by t-dependent test. Clinical parameter data for gingival index, pocket depth and loss of attachment level before and after treatment were tested with Wilcoxon.

3. Results and Discussion

Difference of IL-6 levels and clinical parameters of gingival index, pocket depth and loss of attachment level before and after treatment subgingival application of 4% mangosteen peel extract and placebo gel can be seen in table 1,2,3,4.

Table 1: IL-6 levels and the mean value of decrease before and after treatment in each group.

Group	IL-6. levels		Average value $\bar{x} \pm SD$ ($\mu\text{g/ml}$)	P value
	Before treatment $\bar{x} \pm SD$ ($\mu\text{g/ml}$)	After treatment $\bar{x} \pm SD$ ($\mu\text{g/ml}$)		
Mangosteen Peel Extract 4% ^a	95.41 \pm 29.88	46.50 \pm 12.11	48.91 \pm 19.89	0.001*
Placebo ^a	84.66 \pm 31.09	75.77 \pm 20.98	8.83 \pm 12.17	0.061

^aT-dependent test.

*significant ($p < 0.05$).

Significant difference in the decrease in the test group 4% mangosteen peel extract, which had a greater mean reduction (48.91 \pm 19.89) than the placebo control group (8.83 \pm 12.17).

The decrease in IL-6 levels after subgingival application of the 4% mangosteen peel extract was significant ($p < 0.05$).

Table 2: Gingival index scores and mean values ($\bar{x} \pm SD$) before and after treatment in each group

Group	Gingival Index Score		Average value of $\bar{x} \pm SD$	P value
	Before treatment $\bar{x} \pm SD$	After treatment $\bar{x} \pm SD$		
Mangosteen Peel Extract 4% ^a	1.44 \pm 0.46	0.22 \pm 0.26	1.22 \pm 0.36	0.006*
Placebo ^a	1.11 \pm 0.41	0.55 \pm 0.30	0.55 \pm 0.16	0.004*

^aWilcoxon test.

*significant ($p < 0.05$)

There was a significant difference in the clinical parameter score of the gingival index in the 4% mangosteen peel extract group which had a greater mean reduction (1.22 \pm 0.36) than the placebo control group (0.55 \pm 0.1667). There was a

significant decrease in the gingival index score after subgingival application of the 4% mangosteen peel extract ($p < 0.05$).

Table 3: Score Differences in Clinical Parameters Decrease in Pocket Depth before and After Treatment in Each Group.

Group	Pocket Depth		Average value $\bar{x} \pm SD$	P value
	Before treatment $\bar{x} \pm SD$	After treatment $\bar{x} \pm SD$		
Mangosteen Peel Extract 4% ^a	6.22 \pm 0.66	4.44 \pm 1.50	1.77 \pm 0.97	0.007*
Placebo ^a	6.22 \pm 0.44	6.11 \pm 0.33	0.11 \pm 0.33	0.317

^aWilcoxon test.

*significant ($p < 0.05$)

There was a significant difference in the decrease and significance in the clinical parameter score of pocket depth in the 4% mangosteen peel extract group having a greater mean decrease (1.77 \pm 0.97) than the placebo control group (0.11 \pm

0.33), the decrease in pocket depth score after subgingival application of 4% mangosteen peel extract was significant ($p < 0.05$).

Table 4: Scores of differences in the decrease in attachment level loss before and after treatment in each group.

Group	Losing Attachment Level		Decreasing Average $\bar{x}\pm SD$	P value
	Before treatment $\bar{x}\pm SD$	After treatment $\bar{x}\pm SD$		
Mangosteen Peel Extract ^a	6.22 \pm 1.394	4.89 \pm 1.45	1.33 \pm 0.50	0.006*
Placebo ^a	6.56 \pm 1.333	6.44 \pm 1.13	0.11 \pm 0.33	0.317

^aWilcoxon test.*significant ($p < 0.05$)

Significant difference in the decrease in clinical parameter scores for loss of attachment level in the 4% mangosteen peel extract group experienced a greater mean reduction (1.33 \pm 0.50) than the placebo group (0.11 \pm 0.33), the decrease

in the score for loss of attachment level after subgingival application of 4% mangosteen peel extract was significant ($p < 0.05$). Correlation test of IL-6 concentration to decrease in clinical parameters is shown in Table 5.

Table 5: Correlation between IL-6 levels and clinical parameters of gingival index, pocket depth and loss of attachment level.

IL-6 levels	Parameter	R	P
		Gingival index ^a	0.48
	Pocket depth ^a	0.50	0.02*
	Loss of attachment level ^a	0.26	0.12

^aSpearman correlation test.*significant ($p < 0.05$).

The results of the analysis there was a positive, strong and significant correlation between IL-6 concentration correlated with clinical parameters (Gingival Index, pockets depth and loss of attachment level (Table 5). This study showed the test group given 4% mangosteen peel extract had a greater mean reduction (48.91 \pm 19.89) than the placebo control group (8.83 \pm 12.17). Statistically, the decrease in IL-6 levels after administration of the 4% mangosteen peel extract was significant ($p < 0.05$). This is in line with the theory from *in vitro* studies which states that the reported anti-inflammatory activity of xanthenes in mangosteen, namely α -MG can attenuate lipopolysaccharide (LPS) induced by inflammatory mediators such as tumor necrosis factor (TNF- α) and interleukin-6. α -MG also decreased the activation of several signaling pathways including IL-1. This is also in line with research conducted by Jefferson *et al.* which stated that the pericarp of *G. mangostana* L, showed serotonin-2A (5-hydroxytryptamine-2A) [5, 7, 12]. This study also showed the test group was given 4% mangosteen peel extract on clinical parameters such as gingival index, pocket depth and loss of attachment level had a greater mean reduction than the placebo control group. Statistically, there was a significant decrease in clinical parameter scores after administration of the 4% mangosteen peel extract ($p < 0.05$). The decrease in clinical parameters of pocket depth in the mangosteen peel extract group experienced an average decrease of 1.77 \pm 0.97 compared to the placebo group, which was 0.11 \pm 0.33. The decrease in clinical parameters of the gingival index in the mangosteen peel extract group experienced a greater average decrease with a value of 1.22 \pm 0.36 compared to the placebo group, namely 0.55 \pm 0.16 and also in the clinical parameter group, loss of attachment level, there was a decrease with a value of 1.33 \pm 0.50 compared to the placebo group, namely 0.11 \pm 0.33. Statistically, there was a significant decrease in the mean clinical parameters after administration of mangosteen peel extract ($p < 0.05$). These results are also in accordance with the theory from *in vivo* studies which showed that the anti-inflammatory effect of xanthenes mangosteen peel extract 1-isomangostin, or mangostin triacetate had anti-inflammatory and anti-inflammatory activity. Mahendra *et al.* study found a large decrease in the gingival index in the mangosteen peel extract group (34.27%) compared to the placebo group (53.76%) [5, 13, 15, 16]. The results of the correlation test in this study indicate that there is a strong

positive correlation in the mangosteen peel extract group with gingival index, pocket depth and loss of attachment level. The results of this study are in line with the research conducted by Mahendra *et al.* which was carried out on 50 subjects and the results studies have shown that gel containing 4% mangosteen peel extract can reduce periodontal inflammation, decreased clinical parameters of gingival index, loss of attachment level, and pocket depth were statistically significant [5].

4. Conclusion

Subgingival application of 4% mangosteen peel extract gel as an adjunct therapy for scaling and root planning has been shown to be effective in reducing IL-6 levels and clinical parameters of gingival index, pocket depth and attachment loss in periodontitis stage III grade B patients.

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