Effectiveness Anti-Inflammatory Activity of Mangosteen Rind Extract as an Adjunct Therapy of Chronic Periodontitis

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Abstract

Mangosteen (Garcinia mangostana L.) contains various bioactive components, such as phenolic acid, tannin, xanthone, anthocyanins, and pectin which has various biological effects, such as anti-inflammatory. The aim of this study is to determine the effectiveness anti-inflammatory activity of mangosteen rind extract as an adjunct therapy of chronic periodontitis.

Pubmed NCBI, Cochrane Library, and hand searching databases are searched for studies with the inclusion criteria that discussed the effectiveness anti-inflammatory activity of mangosteen rind extract as an adjunct therapy of chronic periodontitis from 2010 to 2020. A total from 96 articles, six selected articles were reviewed. All articles stated good results in all test groups with greater reduction compared with control groups on all parameters. Variability of the result are likely due to differences in the time, sample inclusion criteria, measurement of the parameters and method of giving mangosteen fruit. Based on the results, it can be seen that the mangosteen rind extract has an anti-inflammatory activity which can be used as an adjunct therapy for chronic periodontitis.

Mangosteen rind extract has an anti-inflammatory activity and effective as an adjunct therapy of chronic periodontitis.

Review (J Int Dent Med Res 2022; 15(4): 1845-1854)

Keywords: Mangosteen, anti-inflammatory, adjunctive therapy, chronic periodontitis.

Received date: 27 September 2022 **Accept date:** 26 October 2022

Introduction

Periodontitis is an inflammatory disease in the supporting tissues of the teeth that impacts the progressive destruction of the periodontal ligaments and alveolar bones. The clinical sign of chronic periodontitis is the presence of inflammation in the gingiva accompanied by swelling, changes in gingiva color, bleeding on probing (BOP) positive, deep pocket formation, loss of attachment, and teeth mobility.[1] According to WHO, severe periodontal disease was estimated to affect nearly 10% of the global population[2]. The prevalance of chronic periodontitis in the adult population worldwide is 30-35%, while in Indonesia is 73,1%[3]. The most important etiological factor of periodontitis is dental plaque[4].

Periodontitis treatment can be performed by mechanical, chemical, or both. Mechanical therapy that can be performed in periodontitis treatment i.e., scaling, rootplaning, and gingival curettage[5]. Pharmacological therapy can also be used as an additional treatment in periodontitis therapy according to the severity of the disease. Usable pharmacological therapy such as, antimicrobial (antiseptic and local or systemic antibiotic), probiotics, and host modulation[6,7].

Currently, alternative therapies derived from herbal plants are known to potentially as an effective source of supplemental drugs[8]. Studies stated that the use of herbal products in controlling gingivitis has lower side effects and is usually more affordable than synthetic products[9]. Mangostana (*Garcinia mangostana L.*) is one of the tropical fruits that are widely used as a traditional drug in Southeast Asia[10]. Mangosteen has the use of preventing pathological disorders associated with oxidative and inflammatory stress[11]. Mangosteen has bioactive components, such as phenolic acid,

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tannin, xanthone, anthocyanins, and pectin[12]. Xanthone contained in the mangosteen rind role as an anti-oxidant, anti-tumor, anti-allergic, anti-fungal, and anti-viral[13,14]. This anti-inflammatory activity contained in the mangosteen rind can be used as an additional treatment of chronic periodontitis.

Materials and methods

The type of research conducted is rapid review, which synthesizes findings and assesses the validity of research used a shortened systematic review method to produce evidence[15]. Databases used in this study are PubMed NCBI, Cochrane Library, and search used hand searching on other sources that had been validated with keywords: Mangosteen, anti-inflammatory, adjunctive therapy and chronic periodontitis.

The inclusion criteria in this study are the article published in 2010-2020 from the PubMed NCBI database, Cochrane Library, and hand searching on other sources that had been validated; the scopus indexed articles for international journals and SINTA for national journals; English and Indonesian articles; and the article that fulfill keywords, while for the exclusion criteria in this study are articles that are not available in full-text, articles that do not discuss the anti-inflammatory influence of mangosteen rind extracts on chronic periodontitis, and narrative articles. The intervention in this study is application of mangosteen fruit rind extract gel comparing to without application of mangosteen fruit rind extract gel. The aim of this study is to find out the influence of anti-inflammatory activity of gel extract mangosteen fruit as an additional treatment of chronic periodontitis.

Article search is done using advanced search using Boolean Operators ""AND"" and ""OR"" on all databases with specified keywords and adjusted to inclusion and exclusion criteria[16]. To complete search, also search manually. Research was conducted online with the research procedure uses PRISMA analysis (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[17]. PRISMA's flow chart as an article selection process can be seen in Chart 1.

The level of evidence in each selected article is assessed based on the Strength of Recommendation Taxonomy (SORT). Level of Evidence is used to show the validity of a study based on the assessment of research design[18].

Results

There are 96 selected articles from searches done through databases or manually. After double article checks, 95 articles are obtained. After reading the title and abstract of each article, 89 articles are excluded and left 6 articles. Of the 6 selected articles, the article is read in its entirety and obtained the final results of 6 articles included in the inclusion criteria in this study.

Characteristics of the article that included the inclusion criteria are presented in Table 1. All samples studied (100%) follow the research procedure until the end. There is only one article that inclusions patients with systemic conditions. Of the 6 articles reviewed, there are 2 articles that used randomized control trial study design[4,19]. One article used clinical trial design[5]. Two articles used animal research study design[20,21]. One article used laboratory study design[22]. Three articles with randomized control trial and clinical trial study design are at level 1, known as Good-Quality with Patient-oriented evidence[4,5,19]. Three articles with analytical research design and laboratory study could not be determined using SORT[20,21,22].

All articles express good results in all test groups with greater reduction of control groups on all assessment parameters even though the value is different. Giving of mangosteen fruit is given locally and systemically. The results of each article are presented on Table 1.

Discussion

Pharmacological therapy can be used as an additional treatment in chronic periodontitis therapy, one of which is anti microbes[1]. Anti microbes that are currently used as gold standard in chronic periodontitis treatment are chlorhexidine 0.2% used as mouthwash, but the use of chlorhexidine 0.2% has some disadvantages, such as can be discolorated on teeth and tongue dorsum, disorders in flavorings, and ulceration in oral mucosa[23].

Therefore, there are many studies that discuss to use herbal plants because it is considered to have no side effects, economic, and easy to obtain so it can be used as adjunctive therapy[24].

Mangosteen fruit (*Garcinia mangostana L.*) is currently widely discussed and used in dentistry, such as inhibiting inflammatory gingiva and as an additional treatment of scaling and rootplaning in periodontal disease[8,19]. Gel extract of mangosteen fruit rind is known to be one of the additional treatments in chronic periodontitis treatment before surgical treatment applied after initial scaling and rootplaning treatment.

In this study, we discussed the biological activity of mangosteen fruit as anti-inflammatory. Based on the results of the research from the three articles, there were reduction differences in all assessment parameters due to differences in study design, research time, sample inclusion criteria, how to measure the assessment parameters and how to give mangosteen fruit[4,5,19]. One of the six articles studied used quasi-experimental study design with split-mouth as a method in its research[5]. One of the main advantages of split-mouth study was that each subject had its own control so as to eliminate variability between subjects, but the disadvantage was, when there was intervention done in one area then it would affect the other area systemically so as to reduce the effect of treatment[9].

Four out of 6 articles apply gel extract of mangosteen rind locally so that significant reduction in PPD and CAL compared to application systemically[4,5,19]. Gel administration of mangosteen rind extract was done locally allowing the concentration of active substances that enter into periodontal pockets to be higher and longer[4,5,19]. In addition, substance insertion will be easier into periodontal pockets and further enhancing patient compliance and was considered safer than systemic applications[9]. One of 6 articles provide intervention to the samples by consuming mangosteen fruit regularly twice a day for three months. The anti-inflammatory effect derived from mangosteen fruit meat would be less compared to the administration in the form of gel extract of mangosteen fruit. This was due to the content of xanthones which had anti-inflammatory activity in the meat of mangosteen fruit less than its rind[19].

Based on the results of the breach, it is known that mangosteen fruit rind extract gel has anti-inflammatory activity. Research conducted by Mahendra et al. (2017)[4] stated that mangosteen fruit rind extract gel can have vasoconstriction effects and can modulate the host inflammatory response so that there is a reduction of PDD due to the reduction of tissue and inflammatory reduction of gingiva. Jean et al. (2020)[19] also stated that there is vitamin C, xanthone, anti-inflammatory, and anti-bacterial content contained in mangosteen fruit can lower the bleeding score. This result was supported by research conducted by Rassameemasmaung et al. (2008)[25] which stated that the mangosteen rind extract gel can modulate the host inflammatory response and tannin content present in mangosteen fruit rind can cause PPD reduction due to its astrigent properties accompanied by contraction and wrinkle tissue and vasocontractor effects that can reduce local edema, exudation, and inflammation.

Presetya et al. (2013)[20] in his research showed that mangosteen rind extract can lower the expression of COX-2 in rats of periodontitis-induced wistar. Xanthone, the main compound found in mangosteen rind acts as an anti-inflammatory role by playing an important role in the cessation of inflammatory activity by inhibiting the production of cycloocygenase enzyme (COX) that is responsible for inflammatory formation. Inhibition of this enzyme triggers the release of prostaglandins that minimize excessive inflammatory response[26]. Results of Sung et al. (2019)[21], stated mangosteen rind extracts can inhibit the expression levels of inflammatory mediators such as, PGE2, iNOS, MMP-8, IL-8, COX-1, and COX-2 significantly.

In addition to lowering the inflammatory process of chronic periodontitis, mangosteen fruit rind extract gel can also decrease the presence of plaque in the oral cavity with a decrease in the plaque index than in the reviewed article. Plaque is known to be the cause of chronic periodontitis. This is due to the presence of anti-microbial activity in mangosteen fruit extract gel. The results of the study conducted by Mahendra et al. (2017)[4]

stated that there was a reduction of the presence of red complex microorganism (RCM): *Treponema denticola* (Td) in a significant test group that was in harmony with the results of the study conducted by Hendiani et al. (2015)[27] that the use of mangosteen fruit extract gel can inhibit the growth of bacteria that are battericidal red complex microorganism (RCM): *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*.

Based on the results of research from the three articles, it could be known that mangosteen fruit rind extract gel has anti-inflammatory activity that can be used as an additional treatment of chronic periodontitis and has anti-bacterial activity that can inhibit the presence of red complex microorganism (RCM) causes periodontal disease, such as chronic periodontitis. Therefore, it is important for clinicians to know that herbal products without relevant side effects can help control the progression of periodontal disease[9].

Conclusions

Gel extract of mangosteen fruit has an anti-inflammatory influence in the additional treatment of chronic periodontitis after initial scaling and rootplaning treatment. In addition, mangosteen fruit rind extract gel can also reduce inflammatory mediators such as, PGE2, IL-6, IL-8, iNOS, MMP-8, COX-1, COX-2, Glycoprotein ALP, and alveolar bone decline. Locally, mangosteen rind extract gel application is known to be more profitable than systemic applications. However, further research is needed with a wider number of samples and research variables for more accurate results so that this mangosteen fruit rind extract can be widely used as an additional treatment for chronic periodontitis.

Acknowledgements

The author thanked to Dr. Drg. Irna Sufiawati, Sp. PM, drg. Faisal Kuswandani, S.Si., Apt, and drg. Anne Agustina Suwartiani, M.KM from Faculty of Dentistry, Universitas Padjadjaran who had given the advices and input in this study.

Declaration of Interest

The authors report no conflict of interest.

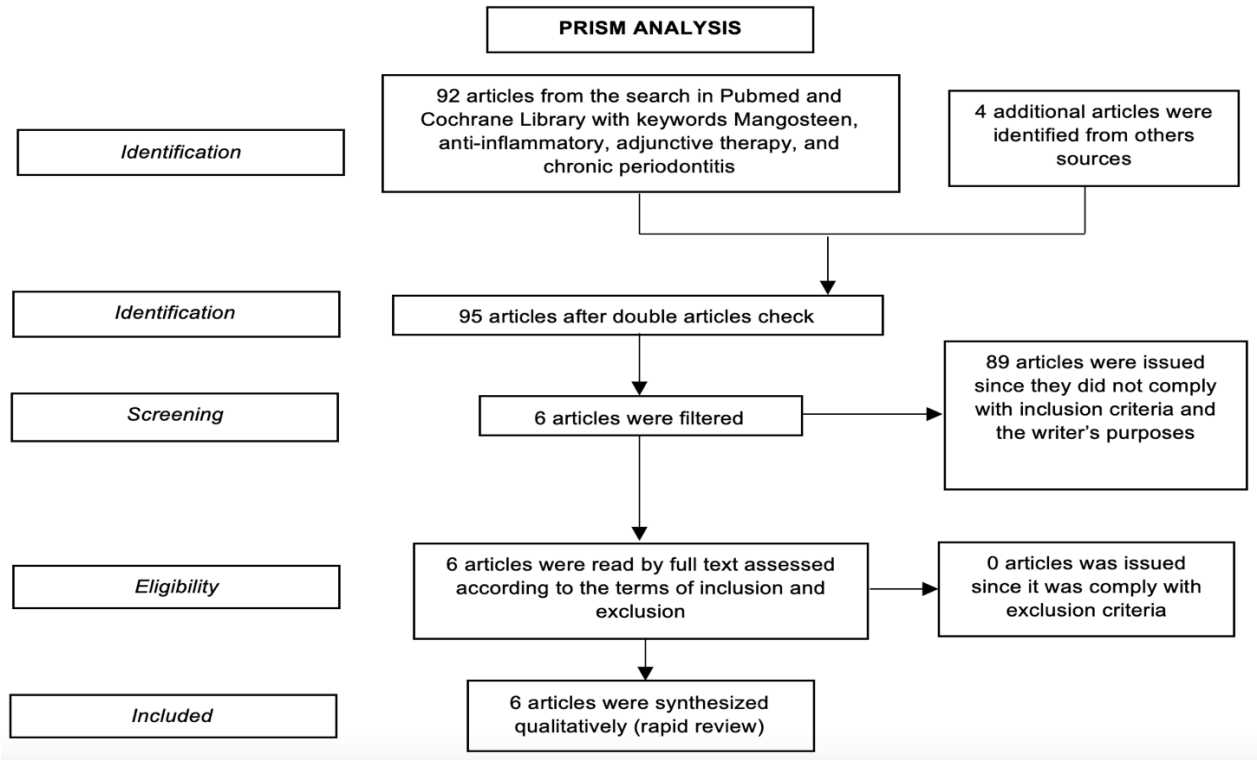

Chart 1. PRISM charts.

Author, Years	Research Time	Research Samples	Assessment of Parameters	The Results	Conclusion
Jaideep Mahendra *et al.*, 2017	3 months	50 patients, 27 male and 23 female, 30-65 years old was divided into two groups: *1.* 25 PG patients *2.* 25 *MGA Group patients* Inclusion Criteria: 1. *Generalized chronic periodontitis* with pocket t ≥ 5mm. 2. Could perform OH to the maximum after initial treatment phase. Exclusion Criteria 1. Patients had aggressive periodontitis. 2. Had Systemic Disease. 3. Allergies to placebo/MGA gel. 4. Pregnant and breastfeeding. 5. Took Steroids for a long time. 6. Smoking. 7. Consuming alcohol. 8. Immunocompromised Patient. Take antibiotics/periodontal therapy in 6 months. Research materials: 1. Gel MGA 4%, 10mg/ml *2.* Gel *placebo* The treatment was given after SRP treatment 3 times in 3 months (1, 2, and 3 months)	*1. PPD* *2. CAL* *3. BI* *4. PI* *5.* The existence of *RCM* *1) Td* *2) Pg* *3) Tf*	*Placebo group:* 1. *Baseline (mean ± SD)* 1) *PPD = 6,65 ± 1,161* 2) *CAL = 6,49 ± 1,329* 3) *BI = 92,147 ± 10,310* 4) *PI = 2,001 ± 0,409* 2. 3rd month *(mean ± SD)* 1) *PPD = 4,11 ± 0,639* 2) *CAL = 4,32 ± 1,031* 3) *BI = 53,76 ± 10,627* 4) *PI = 1,08 ± 0,221* *MGA group* 1. *Baseline (mean ± SD)* *1) PPD = 6,65 ± 1,207* *2) CAL = 6,99 ± 1,303* *3) BI = 91,03 ± 10,031* *4) PI = 1,991 ± 0,347* 2. *3rd month (mean ± SD)* 1) *PPD = 2,90 ± 0,518* 2) *CAL = 3,10 ± 0,881* 3) *BI = 34,27 ± 7,991* 4) *PI = 1,04 ± 0,320* The Existence of *RCM:* 1) 8 samples showed the existence of *Td (MGA Group)* 2) 20 samples showed the existence of *Td*. *(PG)* 1. *Pg* and *Tf* was not detected both in *baseline* nor in the 3rd month.	Giving the 4% of local MGA gels into periodontal pockets in patients with chronic periodontitis could significantly lower PPD, PI, BI, and CAL. In addition, MGA gel could also reduce one of the red complex microorganisms (RCM), which was Td within 3 months significantly.
Ina Hendiani dkk,	1 month	14 chronic periodontitis patients with inclusion criteria:	*1. PPD* *2. GI* *3. BOP*	*Control area* 1. Before treatment: *1) PPD:* M = 5,42; D = 5,43	Application and irrigation of

2017		1. 30-65 years old. 2. There were at least 2 sides with a minimum of 2 teeth involved on each side. 3. The depth of the pocket ≥ 5 mm. 4. Not taking antibiotics for the last 3 months. Exclusion Criteria 1. History of systemic disease 2. Smoking habit Research Materials 1. Extract mangosteen fruit peel gel Samples were treated once during the study, namely at the beginning of the study after SRP.	*4. CAL*	*2) GI:* M = 2,04; D = 2,04 *3) BOP:* M = 1; D = 1 *4) CAL:* M = 6,46; D = 6,04 2.After treatment: *1) PPD:* M = 4,33; D = 4,24 *2) GI:* M = 1,58; D = 1,57 *3) BOP:* M = 0,83; D = 0,87 *4) CAL:* M = 5,79; D = 5,77 *Test area* 1. Before treatment: *1) PPD:* M = 5,61; D = 5,46 *2) GI:* M= 1,90; D = 1,92 *3) BOP:* M = 1; D = 1 *4) CAL:* M = 6,32; D = 6,38 2. After treatment: *1) PPD:* M = 3,55; D = 3,71 *2) GI:* M = 1,03; D = 1,08 *3) BOP:* M = 0,48; D = 0,33 *4) CAL:* M = 4,48; D = 4,79	mangosteen rind extract gel could decrease PPD, GI, BOP, and improved clinical epithelium attachment in chronic periodontitis patients. In addition, mangosteen rind extract could be used as an additional treatment after scaling and rootplaning treatment in chronic periodontitis patients.
S. Catherine Jean *et al.*, 2020	3 months	60 patients in 30-55 years old with an inclusion criteria: 1. Patients with chronic schizophrenia and under antipsychotic treatment for at least 2 years with the same positive and negative syndrome. 2. Periodontitis patient with *PDD of* 4-5 mm in >30% area. 3. Patient within >20 years old. Exclusion criteria 1. Patient with medical/disability disorders 2. Risk of hurting themselves or other people 3. In *intial periodontal therapy treatment for last 6 months* 4. Digestive problems, allergies to mangosteen or latex fruits. 5. Smokers 6. Consumed antibiotics and NSAID for last 6	*1. PI* *2. BI* *3. PPD* *4. CAL*	Group I 1. *Baseline* 1) *PI* = 2.4 2) *BI* = 2.64 3) *PPD* = 5.21 4) *CAL* = 4.90 2. Before treatment *1) PI* = 0.9 *2) BI* = 1.05 *3) PPD* = 4.74 *4) CAL* = 4.43 Group II 1. *Baseline* 1) *PI* = 2.14 2) *BI* = 2.62 3) *PPD* = 5.26 4) *CAL* = 4.88 2. After treatment 1) *PI* = 0.8 2) *BI* = 0.56 3) *PPD* = 4.50 4) *CAL* = 4.12	The consumption of mangosteen fruit could be used as an additional treatment after SRP in patients with chronic schizophrenia because it could reduce periodontal inflammation by effectively reducing bleeding.

		months Patients were divided into 2 groups: 1. Group I: 30 patients who were only given SRP. (Control group) 2. Group II: 30 patients who consumed mangosteen for 2 times a day as an additional treatment of SRP. Research material: 1. Mangosteen, 200 mg. The samples consumed mangosteen for two times a day for three months. The samples consumed mangosteen after SRP treatment.			
Rendra C P *et al.*, 2013	2 weeks	48 male wistar mice, 2 months old, BB 175-200 grams. Rats were divided into 4 groups: 1. Given a dosage mangosteen rind extract of 60 mg/kg. (Test group 1) 2. Given a dosage mangosteen rind extract of 30 mg/kg. (Test group 2) 3. Given ibuprofen of 9 mg/kg BB. (Positive control) 4. Given saline and of 0,5 ml. (Negative control) The samples were given treatment for three times per oral with *oral gauge*. Research materials 1. Mangosteen rind extract, 200 mg.	Expression of COX-2	1. *Mean Rank test of Kruskal-Wallis* for the changes of percentation score in positive area of COX-2: a. Test group 1 = 12,33 b. Test group 2 = 24,33 c. Positive control= 25,50 d. Negative control = 35,83 2. *Mean Rank test of Kruskal-Wallis* for the changes of intensity color score of COX-2: a. Test group 1 = 22,17 b. Test group 2 = 19,25 c. Positive control = 23,92 d. Negative control = 32,67	Mangosteen rind extract was able to lower the expression of COX-2 in rats of periodontitis induced wistar.
Se-Jin Sung *et al.*, 2019	3 weeks	1. *Porphyromonas gingivalis* KCOM 2804. (bacteria and culture cell) 2. 40 male wistar rats weighing 250-400 grams divided into 4 Groups: 1. Positive control	1. Sitokin a. PGE_2 b. IL-8 c. iNOS d. MMP-8 e. COX-1 f. COX-	1. Expression of all cytokines reduced in the Lig+L+MEC Group 1:34 compared to the Lig+L+DW Group. Specifically, iNOS expression decreased 91.1%. 2. The Lig+L+MEC group 1:34 is the most effective group inhibiting the expression levels	*MEC (Mangosteen Extract Complex)* could be used in the prevention and treatment of periodontitis

		group (Non-ligation) 10. 2. Negative control group (Lig+L+DW) 10. 3. Group with provided 8g powder of mangosteen rind extract and 544g propolis extract (Lig+L+MEC 0.5:34) 10. 4. Group with provided 16g powder of mangosteen rind extract 544g propolis extract t (Lig+L+MEC 1:34) 10. The samples were given treatment orally and with feeding needle. Research material: 1. Mangosteen rind extract and propolis	2 2. *Alvolar bone loss* assessment 3. Distance assessment between CEJ and *coronal plane* from *alveolar bone crest*	of all cytokines in the gingival tissue of the mouse model that had been induced periodontitis. 3. Alveolar bone loss was reduced in Lig+L+MEC Group 1:34 and Lig+L+MEC 0.5:34 compared to Lig+L+DW Group. 4. The distance between CEJ and ABC was reduced by 13% and 4.2% in Groups with Lig+L+MEC 1:34 and Lig+L+MEC 0.5:34 compared to Lig+L+DW Group.	
Yun Kyong Lim *et al.*, 2019	2 weeks	1. Porphyromonas gingivalis KCOM 2804 LPS 100ng/ml (bacteria and culture cells) 2. Immortalized Human Gingival Fibroblasts HTERT-hNOF. (Cell viability test) 3. Human Osteoblast-like cell line MG-63 is derived from human osteosarcoma. (Alkaline phosphates activity test) 4. Experimental Groups were divided into 8 Groups: 1. Control group (1% DMSO) (KK negative) 2. Group 1 (1.0 g/ml mangosteen extract, *Mangosteen Extract Complex* (MEC) 1:0) 3. Group 2 (0.5 g/ml mangosteen extract, MEC 0.5:0) 4. Group 3 (34 g/ml propolis extract, MEC 0:34) 5. Group 4 (17 g/ml	1. Sitokin 1) IL-6 2) IL-8 3) PG E_2 2. *Glycoprotein ALP*	1. IL-6 expression decreased 13.5-14.5% in Group 1, 5, and 6 compared to positive KK. 2. IL-8 expression decreased 23.3-26.2% in Group 1 and 5 compared to positive KK. 3. PGE2 expressions could be significantly inhibited (30.3-84.9%) in Groups 3-8. 4. Mineralization levels increased significantly by 9.3-37.4% in Group 1, Group 3, 5-8 including positive KK. 5. RUNX2 expression increased significantly in Group 2, 5, and 7 compared to the negative control group on days 4 and 8. 6. OSX expression was significantly higher in Groups 1-4 than negative KK. 7. COL1A1 expression declined 15.4-8.0% on day 8 compared to negative KK. 8. OCN expression increased 24.2-64.9% on the 8th day in Group 1, 2, 4, and 8.	Mangosteen is a natural product that does not have cytotoxicity in hTERT-hNOF cells. The combination of extract 1 g/ml mangosteen and 34 g/ml propolis has high effectiveness as anti-inflammatory and bone formation agent in vitro. The combination of both can potentially be in the prevention and treatment of periodontal disease.

propolis extract, MEC 0:17)
6. Group 5 (1.0 g/ml mangosteen extract and 34g/ml propolis extract, MEC 1:34)
7. Group 6 (1.0 g/ml mangosteen extract and 17 g/ml propolis extract, MEC 1:17)
8. Group 7 (0.5 g/ml mangosteen extract and 34g/ml propolis extract, MEC 0.5:34)
9. Group 8 (0.5 g/ml mangosteen extract and 17 g/ml propolis extract, MEC 0.5:17)
10. Positive control group 10ng/ml rhBMP2 (to assest *bone formative effect*) (KK positive)

Research material
1. Mangosteen rind extract and propolis

Table 1. Characteristics from the article in inclusion criteria.
PPD: probing pocket depth, CAL: clinical attachment level, BI : bleeding index, PI : plaque index, GI : gingival inflammation, BOP : bleeding on probing (BOP), RCM : red complex microorganism, Td : *Treponema denticola*, Pg : *Pophyromonas gingivalis,* Tf : *Tannerella forsythia*, PG : Placebo Group, MGA : Mangostana Group, Gel MGA : gel mangosteen, M : mesial, D : distal, MEC : *Mangosteen Extract Complex*, OH : oral hygiene, SRP : scaling rootplaning, NSAID : non steroid anti-inflammatory drug, COX-1 : cyclooxygenase-1, COX-2 : cyclooxygenase-2, PGE_2 : prostaglandin E_2, IL-6 : interleukin-6, IL-8 : interleukin-8, iNOS : inducible nitric oxide synthase, MMP-8 : matrix metalloproteinase-8, CEJ : cemento-enamel junction, LPS : lipopolysaccharides, ALP : alkaline phosphatase, ABC : alveolar bone crest, RUNX2 : runt-related transcription factor 2, OSX : osterix, COL1A1 : collagen type 1 alpha 1, OCN : osteocalcin.

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