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Photodynamic Therapy as Adjunctive Treatment of Chronic Periodontitis: A Systematic Review

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ABSTRACT

Background: In the case of chronic periodontitis, conventional mechanical debridement action cannot always eliminate bacteria and toxins in the periodontal pocket. This also can be obtained with additional therapy.
Objective: The aim of this study was to assess the effectiveness of photodynamic therapy (PDT) as adjunctive to scaling and root planing therapy (SRP) in the nonsurgical treatment of chronic periodontitis.
Material and Methods: A systematic search in PubMed, Wiley, and Cochrane were conducted to identify all articles with publication from January 2015 until March 2020 focusing on the effectiveness of PDT as adjunctive therapy in the nonsurgical treatment of chronic periodontitis patients. Searching articles with full-text is done manually, from 454 articles found, there are 20 articles discussed the topic above, then screening the articles were done based on the existing inclusion criteria and the final result was obtained 5 articles that included in this study, had been determined to meet the criteria eligibility. The selected articles are reviewed according to PICO questions.
Results: Out of 5 articles with total 164 patients that met the inclusion criteria, explained that there was a significant change from the assessment of probing depth (PD), clinical attachments level (CAL), bleeding on probing (BOP) in chronic periodontitis treatment with SRP + PDT compared to SRP alone at baseline, 1 month, and 3 months follow up.
Conclusions: Treatment with SRP + PDT as adjunctive therapy is recommended as a modality for the treatment of chronic periodontitis during the maintenance stage in the nonsurgical periodontal treatment.
Keywords: Laser therapy, Photodynamic, Periodontal treatment, Chronic periodontitis
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INTRODUCTION

Chronic periodontitis is a common inflammatory disease that can cause gingival inflammation, resorption of the alveolar bone, the oscillation of teeth, and tooth loss. This disease is largely caused by a subgingival microbiota infection combined with an inflammatory response in the host cell. Periodontitis treatment seeks to remove bacterial biofilms and calculus from teeth and obtain good root surface biocompatibility.[1,2,3,4]

For many years, scaling and root planning (SRP), in combination with a manual scaler using a hand curette and ultrasonic scaler, remains a gold standard in treatment for periodontal disease, and has beneficial results.[5] However, conventional treatments have limitations, such as difficulties in accessing deep periodontal pockets and other anatomical structures.[4,6]

Although there are clinical and microbiological improvements in the majority of cases, at present none of the mechanical instruments is efficient in thoroughly eliminating calculus and bacterial deposits from the periodontal pocket. Antimicrobial chemotherapy is known to suppress periodontal pathogenic bacteria and increase the benefits obtained by conventional mechanical treatment. The inefficiency of some antimicrobial drugs (that is, systemic antibiotics) for drug resistance and side effects such as possible allergic reactions, toxicity, and gastrointestinal complications, should be considered when using these antimicrobial therapies.[4,7]

Photodynamic therapy (PDT), also called photoradiation therapy, phototherapy or photochemotherapy, was introduced in medical therapy in 1904 as inactivation of light-induced cells, microorganisms, or molecules. PDT involves a combination of visible light, usually through the use of a laser diode and a photosensitizer.[7] Photosensitizers are compounds that can to absorb certain light with wavelengths and convert it into useful energy. PDT is recommended as a treatment modality that can reduce the demand for flap surgery, reduce processing time, and the risk of bacteremia. This can also be useful in areas that are difficult to access.[7]

Thus, PDT can represent a promising alternative to reduce bacterial burden or even eradicate certain periodontal pathogens.[8] Photodynamic therapy combines low-level laser light with photosensitizer (a non-toxic dye), which binds to the target cell. Photosensitizers, such as toluidine blue, methylene blue and malachite green, absorb light with a certain wavelength.[4] In an excited state, molecules can react with molecules from the environment, for example with oxygen. Reactive oxygen species can be produced, which can cause oxidative damage to target cells.[6]

Several studies have shown that PDT in addition to SRP is more effective in improving clinical parameters in the treatment of periodontal disease compared to SRP alone.[9,10]

The purpose of this paper is to determine the effect of photodynamic as additional therapy in the management of chronic cases of periodontitis.

MATERIAL AND METHODS

Electronic Pubmed, Wiley Online Library, and Cochrane Library searches were conducted to identify articles published in dental journals from January 2015 until March 2020 which focused in photodynamic therapy as adjunctive therapy in treatment of chronic periodontitis. There are 46 studies that explained about this and with 5 studies met the inclusion criteria. PRISMA guidelines and PICO questions were used in this review.[10,11]

Search Strategy

Initial Pubmed, Wiley and Cochrane Library search of the English language literature were performed to establish a study protocol. The searches were conducted to identify articles published in dental journals from 2015 until 2019 of years which focused in photodynamic therapy as adjunctive therapy in the treatment of chronic periodontitis. The MeSH keywords used were "photodynamic, laser theraphy, periodontal treatment, chronic periodontitis". The search limits applied to the electronic search were the English language, search period, and type of text availability. Manual searches of published full-text articles and related reviews were performed afterward. There are 46 studies explained about this, with only 5 studies met the inclusion criteria. Specific keywords were used to identify the appropriate studies needs and followed the characteristics of PICO questions.[10]

Eligibility Criteria

The inclusion criteria in this study are:

1. Articlespublished in the English language from January 2015 until March 2020.
2. Studies included were clinical study at humans that examined the adjunctive effects of photodynamic/laser therapy in non-surgical periodontal treatment.
3. Participants were patients with the diagnosis of chronic periodontitis were systematically health.
4. The outcome variables included were Probing Depth (PD), Clinical Attachment Loss (CAL), and Bleeding On Probing (BOP) with 1 and/or 3 monthsfollow up.

The exclusion criteria:

1. Studies that did not available in full text.
2. Studied only examined laser therapy as an adjunctive effect in nonsurgical periodontal treatment.
3. Studies only mention one of parameter clinic (PD/CAL/BOP).
4. Potential participants who had any systematic disease or who were under the medication and who had undergone periodontal treatment within the past 6 months.

Selections of Study

Specific keywords were used by 6 participating authors (SO, AR, PT, RF, IF, WW) resulted in the selection of the papers based on the reading of abstract and full-text. Independently, the six investigators selected the paper based on inclusion criteria formerly set. After that, all abstracts and full-texts were downloaded and individually evaluated. The eligibility criteria were used to identify the articles that will be used for this systematic review.

Extraction of Data

The data obtained from sixreviewers through assessment of chronic periodontitis with SRP compared with SRP + PDT and used several clinical parameters such as CAL, PD, and BOP after 1 month and 3 months follow up. All of the full-texts which met the inclusion criteria were read independently by six reviewers and evaluated to formulate this systematic review.

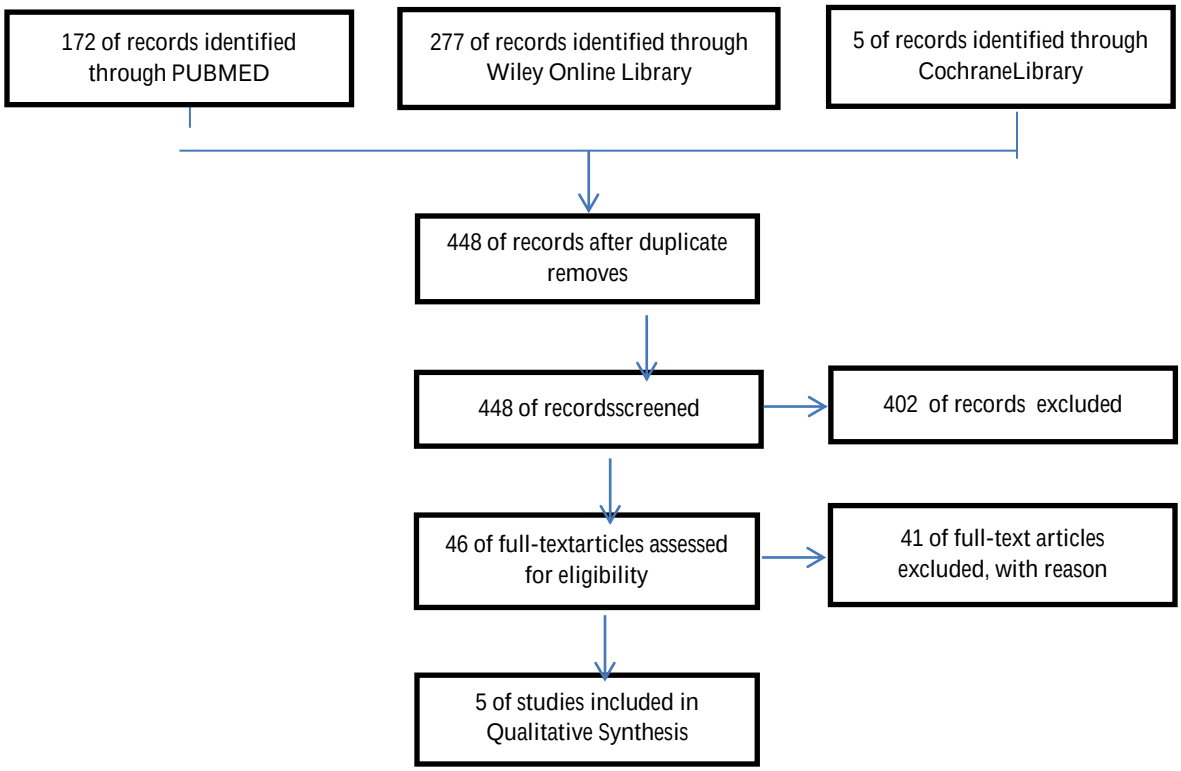

Figure 1: The flow chart of the articles selection

RESULT

In these five articles that fit the eligibility criteria (Table I), it was found that the average patient with chronic periodontitis had an impact on the tissue supporting the teeth, so it was necessary to have proper treatment. Based on the number of samples from this paper there were 173 people involved in this study, with an average age of 18 - 74 years based on existing inclusion and exclusion criteria. Based on the clinical parameters observed, PD, CAL, and BOP. In the control group, patients treated with scaling and root planing, while the test group was patients treated with additional treatments, namely PDT combined with scaling and root planing. The results are then seen at 1 and 3 months after treatment.

The PD, CAL, and BOP clinical parameters showed a statistically significant difference at baseline, 1 month, and 3 months follow up in the test and control groups, although there were several journals did not conduct a BOP examination in that journal. From the 5 articles discussed the effectiveness of photodynamic therapy (PDT) as adjunctive to scaling and root planing therapy (SRP) in the nonsurgical treatment of chronic periodontitis patients, it can be shown in the following table I.

Table I: Assessment of clinical parameters between scaling root planning (SRP) therapy compared with photodynamic therapy (SRP + PDT) as adjunctive to nonsurgical periodontal treatment in chronic periodontitis patients.

No.	Author, Year	Study design	Sample	Age Range	Treatment arms	Clinical Parameter		Evaluation Periode		
								Baseline	1 month	3 months
1.	Carvalho VF et al., 2015. [12]	A randomized controlled clinical trial	34	35-75 years	SRP vs SRP+PDT	PD(mm)	Control	4.87 ± 0.7	-	3.39 ± 0.76
							Test	4.79 ± 0.47	-	3.70 ± 0.85
						CAL (mm)	Control	5.87 ± 1.39	-	4.78 ± 1.44
							Test	5.56 ± 0.83	-	4.61 ± 1.13
						BOP (%)	Control	42.18 ± 19.83	-	17.18 ± 23.66
							Test	58.33 ± 29.70	-	19.44 ± 21.95
2.	SJ Pulikkotil, et.al. 2016 . [9]	Randomized Control Trial	32 years Test : !6 Control: 16	18-60 Years	SRP vs SRP+PDT	PD(mm)	Control	4.95 ± 0.95	4.56 ± 0.65	3.56 ± 0.69
							Test	56.84 ±26.76	4.61 ± 0.65	3.93 ±0.23
						CAL (mm)	Control	5.76 ±1.02	5.21 ± 1.14	4.63 ± 1.23
							Test	5.46 ± 0.63	5.01 ± 0.58	4.48 ± 1.11
						BOP(%)	Control	52.11 ± 21.95	26.54 ± 22.35	19.56 ± 23.35
							Test	56.84 ±26.76	25.64 ± 20.55	12.44 ± 20.45
3.	Abdul Ahad et al. 2016. [13]	A clinical Study	30	-	SRP vs SRP + PDT	PD(mm)	Control	7.53 ± 1.31	6.17 ± 1.20	5.37 ± 0.85
							Test	7.90 ± 1.71	6.27 ± 1.44	5.43 ± 1.36
						CAL (mm)	Control	8.47 ± 1.81	7.53 ± 1.52	6.73 ± 1.31
							Test	8.70 ± 1.91	7.43 ± 1.43	6.67 ± 1.45
						BOP (%)	Control	-	-	-
							Test	-	-	-
4.	PitchanunBundidpun et al. 2017. [14]	A split-mouth randomized clinical trial	20	-	SRP vs SRP+PDT	PD(mm)	Control	4.91 ± 1.02	3.89 ± 1.15A	3.50 ± 1.00A
							Test	4.96 ± 1.11	3.91 ± 1.11A	3.54 ± 0.94A
						CAL (mm)	Control	5.01 ± 1.57	4.35 ± 1.50A	4.17 ± 1.38A
							Test	5.15 ± 1.56	4.46 + 1.49A	4.26 ± 1.33A
						BOP(%)	Control	-	-	-
							Test	-	-	-
5.	Vidal et al. 2017. [15]	Randomized controlled clinical trial	60	33-74 years	SRP vs SRP+PDT	PD(mm)	Control	5.83 ± 1.11	4.34 ± 1.39	3.96 ± 1.20
							Test	5.83 ± 1.11	4.38 ± 1.53	4.19 ± 1.45
						CAL (mm)	Control	6.19 ± 1.42	4.93 ± 1.66*	4.59 ± 1.65*
							Test	6.47 ± 1.60	5.15 ± 2.02*	5.06 ± 1.99*
						BOP (%)	Control	100	49.3*	38.5*
							Test	100	36.4*	41,1*

DISCUSSION

Classical concept of treatment for chronic periodontitis purpose to stop the inflammatory process through sub-gingival biofilm removal. This includes plaque control nonsurgical procedures and SRP followed by surgical therapy wherever indicated. Deep periodontal pockets were selected as these are difficult to be completely debrided by SRP alone due to limited access [13,6]. Photodynamic therapy (PDT) or Laser therapy is a new set of practice that shew necessary as adjunctive periodontal treatment. The laser penetrates the tissues and body fluids and selectively affects the inflammatory mediators [16].

Diode laser helps to reduce subgingivalmicrobiota thus providing sites for new connective tissue attachment. It also helps in the promotion of hemostasis, has detoxifying effects, and enhances healing. Besides that, PDT using methylene blue dye exerts antimicrobial effect, by allowing methylene blue to enter gram-negative bacteria through the porin-protein channels of the outer membrane which upon activation using a diode laser, releases oxidizing metabolites that have harmful effects on lipopolysaccharide[17].

The result of this systematic search of the literature showed had been performed to evaluate the effect of PDT in the treatment of chronic periodontitis. The search of the literature revealed that PDT has been utilized either as an adjunctive therapy. The clinical outcomes of the PDT and SRP were compared with those of SRP alone.

All of the studies included in this review showed a reduction of clinical parameters namely PD, CAL, and BOP after non-surgical therapy. The result indicated that the clinical parameters improve significantly from baseline to 1 and 3 monthsafter treatment interval in both groups. However, there is one study that only showed one-time interval. As well as, both groups resulted in significant improvement in the total number of pockets ≥ 4 mm.

Three studies report that these outcome parameters did not improve statistically significant between the test and control groups. Contradictory, Betsy et al demonstrated that the use of the photosensitizer after SRP significantly reduced PPD and CAL at 3 and 6 months after the treatment compared with SRP alone [18]. Previous studies(Alwaeli et al., 2015) have shown that the SRP + PDT combination benefits clinical parameters to a greater extent than does SRP alone, though other investigators have reported no additional advantage[19,20,21,22].Under experimental conditions, the combination of SRP + PDT did not significantly improve the analyzed clinical parameters. These discrepancies are possibly due to variations in the conditions of PDT application or to the experimental design [21,23,24,25]

Only two studies included the use of PDT revealed significant differences between groups in PD and BOP parameters. Ahad et al in their study showed a combination of SRP and aPDT was more effective in the reduction of PD at 1 month after treatment. Similarly, Pulikkotil et al observed that significant differences of BOP in 1 month compare to the groups.``Chitsazi et al and Crispino et al in their study statethat sites treated with PDT, which had PD of ≥5 mm, showed a greater reduction in PI, CAL, PD, and BOP[22,1].Bundidpun et al found that the test group in a group of periodontal pockets ≥ 4 mm that combined PDT with SRP showing a reduction in the number of probing depth at 76.24%, which higher than the control group which reduced to 75.24%.[14,26,27].

Although, some studies failed to show statically significant benefit in clinical outcomes[23]. Several studies have shown that PDT as an adjunct to SRP was more effective in improving clinical parameters in the treatment of periodontal disease compared with SRP alone [9,28,29]. Antimicrobial photodynamic therapy has been reported to result in additional improvement in clinical parameters of periodontal disease. It is supported by in vitro studies that report the effective killing of periodontal microbes in planktonic and biofilm samples[13]. Besides that, the benefits of PDT as an adjunct nonsurgical treatment are that it can increasingthe patient's comfort and decreasing treatment time.[14]

CONCLUSION

In this systematic review, we conclude that the effect of PDT as adjunctive therapy following SRP can influence several clinical parameters such as PD, CAL, and/or BOP comparing with SRP alone at evaluation period in one month, three months or both. So the treatment of chronic periodontitis with SRP + PDT as adjunctive therapy is recommended as a modality for the treatment of chronic periodontitis during the maintenance stage in the nonsurgical periodontal treatment.

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REFERENCE

1. Crispino A. Effectiveness of a diode laser in addition to non-surgical periodontal therapy: study of intervention. *Ann Stomatol (Roma)*. 2015;(1):15-20. doi:10.11138/ads/2015.6.1.015
2. Wang Y, Li W, Shi L, Zhang F, Zheng S. Comparison of clinical parameters, microbiological effects and calprotectin counts in gingival crevicular fluid between Er:YAG laser and conventional periodontal therapies. *Med (United States)*. 2017;96(51). doi:10.1097/MD.0000000000009367
3. Hokari T, Morozumi T, Komatsu Y, et al. Effects of Antimicrobial Photodynamic Therapy and Local Administration of Minocycline on Clinical, Microbiological, and Inflammatory Markers of Periodontal Pockets: A Pilot Study. *Int J Dent*. 2018;2018. doi:10.1155/2018/1748584
4. Jung GU, Kim JW, Kim SJ, Pang EK. Effects of adjunctive daily phototherapy on chronic periodontitis: A randomized single-blind controlled trial. *J Periodontal*

Implant Sci. 2014;44(6):280-287. doi:10.5051/jpis.2014.44.6.280

5. Annaji S, Sarkar I, Rajan P, et al. Efficacy of photodynamic therapy and lasers as an adjunct to scaling and root planing in the treatment of aggressive periodontitis – A clinical and microbiologic short term study. *J Clin Diagnostic Res*. 2016;10(2):ZC08-ZC12. doi:10.7860/JCDR/2016/13844.7165
6. Berakdar M, Callaway A, Eddin MF, Roß A, Willershausen B. Comparison between scaling-root-planing (SRP) and SRP / photodynamic therapy : six-month study. 2012:2-7.
7. Birang R, Shahaboui M, Kiani S, Shadmehr E, Naghsh N. Effect of nonsurgical periodontal treatment combined with diode laser or photodynamic therapy on chronic periodontitis: A randomized controlled split-mouth clinical trial. *J Lasers Med Sci*. 2015;6(3):112-119. doi:10.15171/jlms.2015.04
8. Sculean A, Schwarz F, Ro R. Photodynamic Therapy as an Adjunct to Non-Surgical Periodontal Treatment : 2008;79(9). doi:10.1902/jop.2008.070652
9. Pulikkotil SJ, Toh CG, Mohandas K, Leong KVG. Effect of photodynamic therapy adjunct to scaling and root planing in periodontitis patients : A randomized clinical trial. 2016:440-445. doi:10.1111/adj.12409
10. Wallace BC, Kuiper J, Sharma A, Zhu M, Marshall IJ, Kuiper J. Extracting PICO Sentences from Clinical Trial Reports using Supervised Distant Supervision. *J Mach Learn Res*. 2016;17:1-25. doi:10.1161/CIRCRESAHA.116.303790.The
11. Moher D. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions : Explanation and Elaboration. 2009;62(10).
12. Carvalho VF, Andrade PVC, Rodrigues MF, et al. Antimicrobial photodynamic effect to treat residual pockets in periodontal patients: A randomized controlled clinical trial. *J Clin Periodontol*. 2015;42(5):440-447. doi:10.1111/jcpe.12393
13. Ahad A, Lamba AK, Faraz F, Tandon S, Chawla K, Yadav N. Effect of antimicrobial photodynamic therapy as an adjunct to nonsurgical treatment of deep periodontal pockets: A clinical study. *J Lasers Med Sci*. 2016;7(4):220-226. doi:10.15171/jlms.2016.39
14. Bundidpun P, Srisuwantha R, Laosrisin N. Clinical effects of photodynamic therapy as an adjunct to full-mouth ultrasonic scaling and root planing in treatment of chronic periodontitis. *Laser Ther*. 2018;27(1):33-39. doi:10.5978/islsm.18-OR-03
15. Segarra-vidal M, Lilian SG, Vallés S, et al. Effects of photodynamic therapy in periodontal treatment : A randomized , controlled clinical trial. 2017;(June):915-925. doi:10.1111/jcpe.12768
16. Teymouri F, Farhad SZ, Golestaneh H. The Effect of Photodynamic Therapy and Diode Laser as Adjunctive Periodontal Therapy on the Inflammatory Mediators Levels in Gingival Crevicular Fluid and Clinical Periodontal Status. *J Dent (Shiraz, Iran)*. 2016;17(3):226-232.
17. Mistry A, Pereira R, Kini V, Padhye A. Effect of combined therapy using diode laser and photodynamic therapy on levels of IL-17 in gingival crevicular fluid in patients with chronic periodontitis. *J Lasers Med Sci*. 2016;7(4):250-255. doi:10.15171/jlms.2016.44
18. Betsy J, Prasanth CS, Baiju K V., Prasanthila J, Subhash N. Efficacy of antimicrobial photodynamic therapy in the management of chronic periodontitis: A randomized controlled clinical trial. *J Clin Periodontol*. 2014;41(6):573-581. doi:10.1111/jcpe.12249
19. Dilsiz A, Canakci V, Aydin T. Clinical Effects of Potassium–Titanyl–Phosphate Laser and Photodynamic Therapy on Outcomes of Treatment of Chronic Periodontitis: A Randomized Controlled Clinical Trial. *J Periodontol*. 2013;84(3):278-286. doi:10.1902/jop.2012.120096
20. Pourabbas R, Kashefimehr A, Rahmanpour N, et al. Effects of Photodynamic Therapy on Clinical and Gingival Crevicular Fluid Inflammatory Biomarkers in Chronic Periodontitis: A Split-Mouth Randomized Clinical Trial. *J Periodontol*. 2014;85(9):1222-1229. doi:10.1902/jop.2014.130464
21. Schwarz F, Aoki A, Becker J, Sculean A. Laser application in non-surgical periodontal therapy: A systematic review. *J Clin Periodontol*. 2008;35(SUPPL. 8):29-44. doi:10.1111/j.1600-051X.2008.01259.x
22. Achmad H, Adam AM, Azizah A, Sukmana BI, Huldani, Khera SN, Ramadhany YF. A Review of Bandotan Leaf Extract (Ageratum conyzoides L.) in Inhibition Test to the Growth of Bacteria (Porphyromonas gingivalis) Case of Periodontitis Disease. Systematic Reviews in Pharmacy. 2020; 11(4): 390-395
23. Chitsazi MT, Shirmohammadi A, Pourabbas R, et al. Clinical and Microbiological Effects of Photodynamic Therapy Associated with Non-surgical Treatment in Aggressive Periodontitis. *J Dent Res Dent Clin Dent Prospects*. 2014;8(3):153-159. doi:10.5681/joddd.2014.028
24. Achmad H, Oktawati S, Adam AM, Pasiga B, Sjahril R, Azizah A, Sukmana BI, Huldani, Siswanto H, Neormansyah I. Granulicatella Adiacens Bacteria Isolation from Perodontitical Patients with Polymerase Chain Reaction Techniques. Systematic Reviews in Pharmacy.2020; 11(4): 394-400
25. Pessoa L, Galvão V, Damante C, Sant'Ana ACP. Removal of black stains from teeth by photodynamic therapy: clinical and microbiological analysis. *BMJ Case Rep*. 2015:bcr2015212276. doi:10.1136/bcr-2015-212276
26. Achmad H, Thahir H, Rieuwpassa I, Mardiana AA, Oktawati S, Samad R, Djais AI, Gani A, Singgih MF, Madjid F, Admy SC. The Effectiveness of Channa striata

Extract Antimicrobial Effect on Periopathogen Bacteria (Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans). Systematic Reviews in Pharmacy. 2020; 11(4): 319-323.

27. Djais AI, Oktawati S, Thahir H, Hatta M, Sukmana BI, Dewi N, Huldani, Inayah Y, Widodo, Riewpassa IE, Achmad H, Dewang D . Effect of the Combination of Demineralization Freeze Dried Dentin Matrix (DFDDM) and Moringa Oleifera Lam on Nuclear Factor Kapa B as a Marker of Bone. Systematic Reviews in Pharmacy. 2020; 11(4): 515-522.
28. Achmad H, Adam AM, Mappangara S, Oktawati S, Sjahril R, Singgih MF, Neormansyah I, Siswanto H. Identification and Antimicrobial Susceptibility of Granulicatella adiacens Isolated from Periodontal Pocket. Systematic Reviews in Pharmacy. 2020; 11(4): 324-331.
29. Djais AI, Oktawati S, Thahir H, Hatta M, Sukmana BI, Dewi N, Huldani, Inayah Y, Widodo, Riewpassa IE, Achmad H, Dewang D . The Effect of the Combination of Demineralization Freeze Dried Dentin Matrix (DFDDM) and Moringa oleifera Lam to increase Fibroblas and Osteoblas cell in Alveolar Bone after Caviacobaya's Tooth Extraction. Systematic Reviews in Pharmacy. 2020; 11(4): 523-530.