

Blue Light Photodynamic Therapy With Curcumin and Riboflavin in the Management of Periodontitis: A Systematic Review



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Abstract

Introduction: The aim of this article was to evaluate reports in the scientific literature that used antimicrobial photodynamic therapy (aPDT) with a blue light source and curcumin and riboflavin as photosensitizers in the management of periodontitis.

Methods: The search was conducted in electronic databases, including PubMed, Web of Science, and Scopus, with the keywords "photodynamic therapy", "antimicrobial photodynamic therapy", "laser activated disinfection", "photoactivated disinfection", "light activated disinfection" "LED", "Periodontitis", "Curcumin", "Riboflavin", and "periodontitis" from 2012 to 2020.

Results: After evaluating a total of 24 relevant articles, 13 articles were selected, full texts were read, and the data were extracted and placed in a table.

Conclusion: Reviewing articles showed that curcumin as a photosensitizer activated by a blue wavelength is effective in the elimination of the various bacterial species involved in periodontal disease, and to the best of our knowledge, there is no study that has shown this substance does not reduce bacteria. According to the result of the articles, riboflavin as a photosensitizer activated by blue light can reduce bacteria that are involved in periodontitis, but other studies have reported that blue light alone can also reduce bacteria significantly. Therefore, more in-vitro and clinical trial studies are needed to give a more conclusive opinion on the effectiveness of riboflavin as a photosensitizer in the treatment of periodontitis.

Keywords: Curcumin; Riboflavin; Antimicrobial photodynamic therapy; Periodontitis; LED.



Introduction

Periodontitis is an inflammatory condition affecting the periodontal tissue, predominantly induced by bacteria placed in the plaque biofilm. Pocket forming in the gum tissue, loss of attachment, bone destruction, and finally possible tooth loss at the end of the infection process are indicators of pathology and progress in the disease process. Periodontitis as the second most prevalent oral disease in the world affects 30%–50% of adults.^{1,2} The initial goal of conventional nonsurgical periodontal therapy is to control microbial periodontal infection by removing bacterial deposits in the supragingival and subgingival biofilm and calculus, through mechanical treatments such as scaling and root planing (SRP) which is considered as a "gold standard" method.³ Complete removal of bacterial deposits and their toxins within the periodontal pockets and from the root surfaces such as furcations, concavities and grooves is not necessarily achieved with conventional

mechanical techniques.⁴ Another option for decreasing bacteria in the management of periodontitis is through chemical agents such as chlorhexidine. Chemical plaque control can enhance the efficacy of mechanical plaque control.⁴

One of the available non-invasive methods for reducing microorganisms located in areas inaccessible to SRP is antimicrobial photodynamic therapy (aPDT).⁵ aPDT is based on three basic components including coloring dye (photosensitizer), light source and oxygen. The mechanism of aPDT is related to generating cytotoxic products such as reactive oxygen species (ROS) which are harmful to bacteria through induced damage to DNA and cell membranes. Rapidness, non-invasiveness and simple manipulation procedures are the main characteristics of this approach, besides offering good results at low costs.⁶

Photosensitizers are usually chemical compounds that can be activated by various wavelengths of light in

order to produce ROS that can damage microorganisms and cancer cells. Recently, such new photosensitizers as curcumin, hypericin and riboflavin that are categorized in a natural compound have been introduced.⁷

Curcumin is a bright yellow chemical obtained from *Curcuma longa* plants. Curcumin has a wide range of advantageous characteristics, including anti-inflammatory, antioxidant, chemopreventive and chemotherapeutic activity. Curcumin can also be used as a photosensitizer for the management of contaminations in the mouth or on the skin. It has antimicrobial characteristic and due to its ability to absorb blue light and the production of ROS, it can be used in photodynamic therapy.^{8,9} This photosensitizer is activated within a range of blue wavelengths, including but mostly with peak absorption of 430 nm.

Riboflavin, also known as vitamin B₂, is a vitamin naturally present in some food products and used as a dietary supplement. Riboflavin is an efficient biocompatible photosensitizer inducing oxidative damage when irradiated with blue light even with the LED lamps used for curing composite restorative materials.¹⁰

Light sources in aPDT include light-emitting diode (LED) (blue or red light) and lasers. The correct choice of a light source depends on the matched absorption wavelength for the specific photosensitizer material used and the target tissue. Different light sources are used in the aPDT system. Laser photonic delivery is coherent and of monochromatic (single) wavelength, but lamps differ through light incoherence and typically deliver a bandwidth of wavelengths.¹¹

To our knowledge, there is no systematic review evaluating the curcumin and riboflavin as photosensitizers activated by blue wavelengths. In addition, the light wavelength, power and energy density and concentration of photosensitizers were heterogeneous. Therefore, the purpose of this article was to review the efficiency of aPDT with a blue light source and curcumin and riboflavin as photosensitizers in the management of periodontitis.

Methods

Study Design

This systematic review is written according to the guidelines in PRISMA.

Focused Research Question

Is the use of curcumin and riboflavin as photosensitizers activated by blue wavelengths in aPDT useful in the removal of the various bacterial species involved in periodontal disease?

Search Strategy

The search strategy was done based on PICO:

Population: patients with periodontitis/periopathogen bacteria

Intervention: photodynamic therapy with curcumin

and riboflavin

Comparison: Control groups receiving another therapy
Outcome: Bacterial reduction

We searched the PubMed, Scopus and Web of Science database engines between January 2012 and September 2020, using the following keywords: “photodynamic therapy”, “antimicrobial photodynamic therapy”, “laser activated disinfection”, “light activated disinfection”, “photo activated disinfection”, “LED”, “periodontitis”, “curcumin”, and “riboflavin”.

Eligibility Criteria

Studies that utilized various wavelengths between 420 to 480 nm of the blue LED were chosen. Studies that used curcumin and riboflavin as photosensitizers with various concentrations were included. Also, studies examining the influence of aPDT by various wavelengths on the counts of gram-positive and gram-negative bacteria involved in periodontal diseases were included. *In vitro*, *ex vivo* and *in vivo* studies, published from January 2012 to September 2020 and reached from the full text of the articles, were included. We chose only clinical studies that evaluated the changes in bacterial counts and excluded studies that evaluated clinical parameters such as bleeding on probing and clinical attachment loss. Furthermore, we did not include literature and narrative reviews, case report, case series, short communications and letters to editors.

Study Selection

Two authors (NCH and MH) independently assessed the selected studies, which were extracted from the database search. In the first phase, the titles and abstracts, and in the second phase, the full texts of manuscripts were assessed. In case of any disagreements between the two authors, a third author (AE) gave his comments.

Data Extraction

Two authors (NCH and MH) extracted the data independently. In case of any disagreements, the third author (AE) was involved. Firstly, 258 articles were found through searching the database. Then the titles and abstracts of the articles were read and 36 articles were selected. The full text of these articles was studied by following the inclusion criteria, where the total of extracted articles was restricted to 13. The articles were assessed and the data including first author, year, type of study, photosensitizer, and light source characteristics were extracted (see [Tables 1 and 2](#)).

Results

After evaluating a total of 24 relevant articles, 13 articles were selected, including 3 *in vivo* and 10 *in vitro* studies. The selection process is shown in [Figure 1](#).

Discussion

The application of conventional non-surgical periodontal

Table 1. Studies on the Application of Curcumin as a Photosensitizer in aPDT in Periodontitis

Author/year	Type	Bacteria	PS (Concentration)	Light Source (Output Power, Intensity, Wavelength, Dose, Time)	Result	Conclusion
Araujo et al, 2012 ¹²	Clinical trial	-	Curcumin 1.5 g/L	Blue light-emitting diode (67 mW/cm ² , 450 nm, 20.1 J/cm ²)	A significant difference was shown between PDT and curcumin alone. The PDT group reduced bacteria statistically significantly but the group treated with photosensitizers alone had no effect on bacteria counts.	Photodynamic therapy is efficient in the reduction of salivary microorganisms. Curcumin alone did not show a significant reduction.
Mahdi et al, 2015 ¹³	In vitro	<i>P. gingivalis</i> , <i>F. nucleatum</i>	Curcumin, hydrogen peroxide, erythrosine	Light emitting diode (LED) device (570 mW/cm ² , 440-480 nm, 2 min)	Blue light-activated curcumin and hydrogen peroxide (2 min) reduced <i>P. gingivalis</i> 100%, but light-activated (4 min) erythrosine eliminated approximately the whole population of <i>P. gingivalis</i> .	A Blue LED in conjunction with curcumin, hydrogen peroxide and erythrosine could serve for the reduction of main periopathogenic bacteria.
Sreedhar et al, 2015 ¹⁴	Clinical trial	-	Curcumin (10 mg/g)	Blue halogen curing light (620 mW/cm ² , 470 nm, 5 min)	Curcumin activated with blue light had significantly higher bacteria reduction in comparison with SRP alone. Several treatments of PDT reduced the bacteria to the minimum amount which was significant compared to single application.	Photodynamic therapy with curcumin is a useful treatment modality adjunctive to conventional SRP.
Najafi et al, 2016 ¹⁵	In vitro	<i>A. actinomycetemcomitans</i>	Curcumin (5 mg/mL)	Blue light LED (400 mW/cm ² , 420-480 nm, 120 J/cm ² , 5 min)	curcumin had a significantly higher minimum inhibitory concentration compared to CHX ($P < 0.05$). CHX, LED + curcumin, curcumin, and LED group showed the lowest to highest bacterial growth respectively.	curcumin is an effective photosensitizer for growth prevention of <i>A. actinomycetemcomitans</i> , especially when activated by LED in the photodynamic therapy process.
Ricci Donato et al, 2017 ¹⁶	Clinical trial	-	Curcumin (25 and 100 mg/L), Photogem (25 and 100 mg/L)	Blue light diode (LED) device (450 nm for Curcumin and 630 nm for Photogem, 100W/cm ²)	Curcumin (100 mg/mL) with 6 min light activation has greater superiority by presenting bacteria reduction immediately after PDT.	Photodynamic therapy using Photogem and Curcumin activated by specific emitting light are promising techniques for the reduction of bacteria in the oral cavity.
Pourhajjibagher et al, 2018 ¹⁷	In vitro	<i>A. actinomycetemcomitans</i>	Curcumin (0.3 to 40 µmol/mL)	Diode LED (1000-1400 mW/cm ² , 450 nm, 60-80, 120-168, 180-240, 252-336, and 300-420 J/cm ² , 1 to 5 min)	Curcumin with more than 10 µmol/mL concentration caused a significant reduction in the growth of bacteria compared to the control group.	Photodynamic therapy with curcumin leads to decreased cell survival and virulence of <i>A. actinomycetemcomitans</i>
Saitawee et al, 2018 ¹⁸	In vitro	<i>A. actinomycetemcomitans</i>	Curcumin	Blue LED Diode (420-480 nm, 16.8 J/cm ² , 1 min)	Curcumin with no light activation did not show a significant reduction in <i>A. actinomycetemcomitans</i> counts. But aPDT with Blue light and Curcumin (0.78 µg/mL) solution produced a complete reduction of <i>A. actinomycetemcomitans</i> .	Curcumin is an effective photosensitizer when activated by blue light in aPDT.
Böcher et al, 2019 ⁴	In vitro	Dental plaque samples	Curcumin (100 mg/L) HELBO Blue Indocyanine green	SLB group: Diode LED (600 mW, 445 ± 5 nm) aPDT group: HELBO TheraLite Laser (665 nm) aPTT group: FOX Q810plus (810 nm)	All treatment groups showed a significant reduction in the bacterial count, but the highest one occurred in the aPTT group (indocyanine green +810 nm).	Curcumin as a photosensitizer activated by 445 nm laser irradiation did not show any significant difference in the bacterial count compared to laser application alone.

Table 1. Continues

Pourhajbagher et al, 2019 ¹⁹	In vitro	A. <i>actinomycetemcomitans</i> , <i>P. gingivalis</i> , <i>P. intermedia</i>	Curcumin (40µM) Graphene quantum dot (100 µg/mL)	Blue LED (435 ± 20 nm, 60–80 J/cm ² , 1 min)	Cur + LED resulted in a significant reduction of the bacteria counts in comparison with the control group.	aPDT with curcumin might be a hopeful therapeutic option for the treatment of periodontal pathogens mixed biofilms.
Mahdizade-Ari et al, 2019 ²⁰	In vitro	<i>A. actinomycetemcomitans</i>	Curcumin (80 µg/mL)	Diode LED (600 mW, 445 nm ± 5 nm, 100 Hz)	aPDT with curcumin could significantly reduce microbial cell survival and metabolic activity.	aPDT with curcumin can be used as an adjunct modality for the management of local infections.
Zago et al, 2020 ³	In vitro	Patients periodontal pocket	Curcumin methylene blue chlorin-e6	Blue LED :450 nm Red LED: 660 nm	12.5 µg/mL curcumin + 30 J/cm ² light dose could significantly decrease the microbial load in the planktonic phase. 100 µg/mL curcumin + 150 J/cm ² light dose could significantly decrease the microbial load in the biofilm phase.	photosensitizers at a suitable concentration associated with specific wavelengths and light intensity proved to be effective in eradicating oral biofilm in periodontal disease.

Table 2. Studies on the Application of Riboflavin as a Photosensitizer in aPDT in Periodontitis

Author/Year	Type	Bacteria	PS	Light Source (Output Power, Intensity, Wavelength, Dose, Time)	Result	Conclusion
Nielsen et al, 2015 ¹⁰	In vitro	(<i>A. actinomycetemcomitans</i> , <i>E. faecalis</i> , <i>E. coli</i> , <i>L. paracasei</i> , <i>P. gingivalis</i> , <i>P. intermedia</i> , <i>P. acnes</i>)	Riboflavin (266 µmol/L)	LED (400 mW, 0.63 W/cm ² , 460 nm, 37.7 J/cm ² , 1 min)	aPDT with riboflavin only results in a minor reduction of bacteria compared to toluidine blue O/red light which results in the full killing of all bacteria species.	Riboflavin as a photosensitizer cannot be suggested to be used for aPDT in the management of periodontitis or endodontic infections.
Bärenfaller et al, 2016 ²¹	In vitro	(<i>P. gingivalis</i> , <i>P. intermedia</i> , <i>A. actinomycetemcomitans</i> , <i>C. rectus</i> , <i>E. corrodens</i> , <i>F. nucleatum</i> , <i>T. forsythia</i> , <i>A. naeslundii</i> , <i>E. nodatum</i> , <i>F. alocis</i> , <i>P. micra</i> , <i>S. gordonii</i>)	Riboflavin (0.1%) Toluidine blue (0.1%)	Blue LED (1 W, 2 W/cm ² , 460±10 nm, 30 and 60 s) Red LED	Riboflavin activated by LED for 30 seconds could not reduce <i>P. gingivalis</i> and <i>P. intermedia</i> but by increasing time to 60 seconds, the bacteria count decreased significantly (<i>P</i> <0.001). Toluidine blue activated with red LED reduced all bacteria counts (<i>P</i> <0.001).	Photodynamic therapy using LED and riboflavin is effective for the elimination of periodontopathogenic microbial species but not as effective as TBO+red LED.

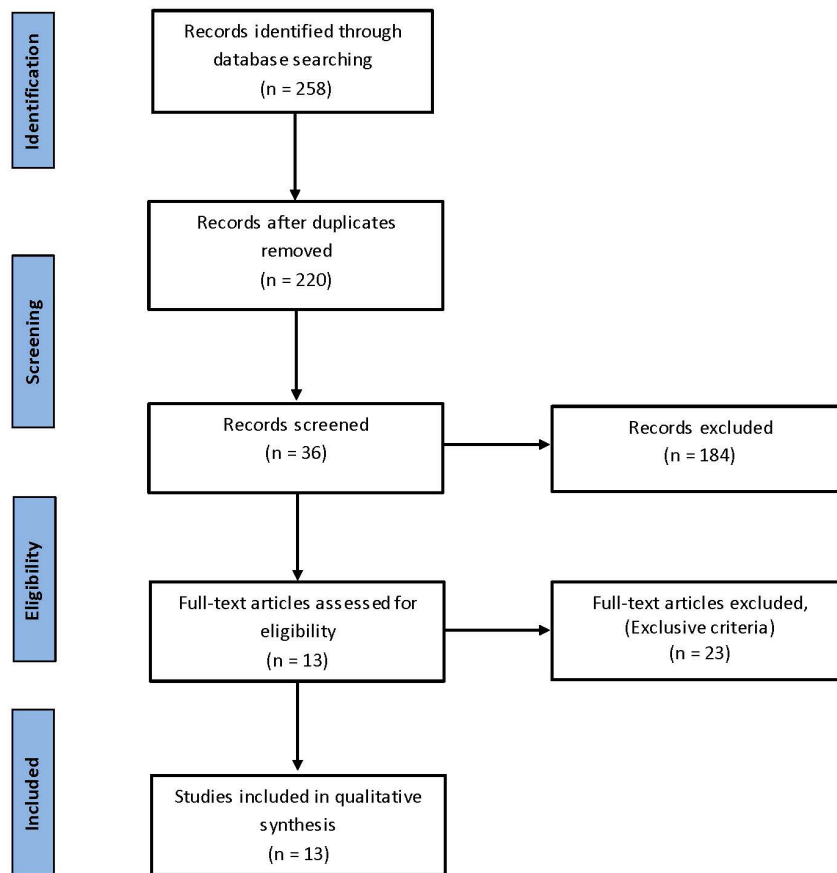


Figure 1. PRISMA flow diagram of studies selected through the search

treatments such as SRP is limited due to subgingival tooth surface morphology, challenging access to furcation and concavities.²² In addition to mechanical therapy, adjuvant treatments like systemic or local antibiotic therapy have been suggested, but due to creating side effects and bacterial resistance when repeatedly applied, new strategies are needed. The use of aPDT has therefore been suggested.⁴

Antimicrobial photodynamic therapy involves a photosensitizing chemical substance which produces a form of oxygen killing nearby microorganisms when it is light-activated. Photosensitizers are activated by a specific wavelength of the light source.²³ Common photosensitizers used in aPDT include methylene blue, toluidine blue O, and indocyanine green, and recently, curcumin and riboflavin have been introduced as a new class of photosensitizers for aPDT.

Curcumin is a hydrophobic photosensitizer that is soluble in *dimethyl sulfoxide* (DMSO), acetone, ethanol, and oils.¹⁷ The mechanism of curcumin-related damage to the bacterial membrane in both gram-negative and gram-positive bacteria has been reported, and it is indicated that curcumin binds to lipid membrane and bacterial proteins and it has shown great potential as a photosensitizer because it is able to absorb blue light and produces ROS.⁹

Riboflavin (vitamin B2) is an efficient photosensitizer inducing oxidative damage when activated with visible light, especially blue light and LED lamps used for curing dental composite. It cannot produce tooth discoloration as severely as TBO due to its bright yellow color, which may be considered an advantage in esthetic regions.²²

One of the important criteria in the success rate of periodontal treatment with aPDT is the species of bacteria. Research has been done on different types of bacteria involved in periodontal disease. Other criteria that contribute to the success of the treatment are the concentration of the photosensitizer substance and wavelength and duration of the light source used in photoactivating the photosensitizer.

Pourhajibagher et al evaluated the in vitro inhibitory effects of antimicrobial PDT with curcumin against *Aggregatibacter actinomycetemcomitans* bacteria and reported that aPDT with curcumin resulted in a significant reduction in bacteria. The result of their study showed that curcumin at concentrations above 5 $\mu\text{mol/mL}$ or 1.2 $\mu\text{mol/mL}$ of curcumin plus four minutes of irradiation time with LED at the wavelength of 450 nm can significantly reduce the *A. actinomycetemcomitans* CFUs/mL.¹⁷ Araujo et al. assessed the efficacy of curcumin activated by the LED device in the bacteria presented

in saliva samples of 13 adult volunteers and stated a significant reduction of microorganisms.¹² Saitawee et al evaluated the photodynamic therapy of curcumin stimulated with blue light LED at a wavelength of 420–480 nm against *A. actinomycetemcomitans* and reported that the bactericidal efficacy of aPDT was dose-dependent. The concentration of curcumin at 0.78 µg/mL showed a significant reduction in the bacterial count.¹⁸

Bärenfaller et al²¹ and Nielsen et al¹⁰ compared the effect of riboflavin and toluidine blue o as photosensitizers against several species of microorganisms including *A. actinomycetemcomitans*, *Porphyromonas gingivalis* and *Prevotella intermedia* that are related to the initiation and progression of periodontitis and reported that riboflavin can eliminate some microorganism species, but TBO has higher antimicrobial activity. According to the result of Nielsen and colleagues' study, *P. gingivalis* and *P. intermedia* were eliminated by aPDT with a blue light source and riboflavin as a photosensitizer and also by blue light treatment alone. Therefore, more in vitro and clinical trial studies are needed to give a more conclusive opinion on the usefulness and effectiveness of riboflavin as a photosensitizer in the treatment of periodontitis.

Sreedhar et al,¹⁴ in a split-mouth clinical study, compared the effect of curcumin alone or accompanied by photo-activation as an adjunct treatment to scaling and root planning in the management of chronic periodontitis; the study reported that curcumin as a local sub-gingival drug could reduce periodontal pathogens such as *A. actinomycetemcomitans*, *P. gingivalis*, and *P. intermedia* significantly and further irradiation with blue light at 470 nm increased the antimicrobial effect of curcumin. In the Araujo and colleagues' study which evaluated the sensitivity of pathogens of salivary flora to curcumin activated by blue light at the wavelength of 450 nm in a clinical trial study, curcumin alone did not produce a potent reduction of microorganisms while photo-activated curcumin produced a statistically significant reduction.¹²

There are more articles on methylene blue which is one of the most commonly used photosensitizers with contradictory results due to different concentrations of dye, different wavelengths of the light source for activation and the treatment protocols^{24–27}; the review articles showed that curcumin as a photosensitizer activated by a blue wavelength is effective in the elimination of the various bacterial species involved in the periodontal disease and to the best of our knowledge, there is no study showing that this substance as a photosensitizer does not reduce bacteria. However, clinical and laboratory results are contradictory as to whether or not curcumin alone as a local drug has an antibacterial effect.

The safety and efficacy of curcumin have been evaluated by clinical trials in humans. Investigations in this field have mainly focused on the anticancer properties of curcumin and its association with light, and its non-toxicity has

been reported.^{28–30} Riboflavin is highly biocompatible and research shows that riboflavin is safe in specific doses and is characterized as 'generally recognized as safe' by the Food and Drug Administration (FDA). Therefore, we recommend more investigations with these two substances as photosensitizers to evaluate their clinical effects on periodontitis in clinical situations.^{10,31}

Conclusion

Curcumin and riboflavin as photosensitizers activated by blue light in the aPDT procedure have the potential for reducing the bacterial count in periodontal infection. More clinical studies are needed to find the best protocol including suitable concentration of Curcumin or riboflavin accompanied by appropriate laser parameters.

Ethical Considerations

Not applicable.

Conflict of Interests

The authors declare that they have no conflict of interest.

References

1. Meisel P, Kocher T. Photodynamic therapy for periodontal diseases: state of the art. *J Photochem Photobiol B*. 2005;79(2):159–70. doi: 10.1016/j.jphotobiol.2004.11.023.
2. Saini R, Marawar PP, Shete S, Saini S. Periodontitis, a true infection. *J Glob Infect Dis*. 2009;1(2):149–50. doi: 10.4103/0974-777X.56251.
3. Zago LHP, de Annunzio SR, de Oliveira KT, Barbugli PA, Valdes BR, Feres M, et al. Antimicrobial photodynamic therapy against metronidazole-resistant dental plaque bacteria. *J Photochem Photobiol B*. 2020;209:111903. doi: 10.1016/j.jphotobiol.2020.111903.
4. Böcher S, Wenzler JS, Falk W, Braun A. Comparison of different laser-based photochemical systems for periodontal treatment. *Photodiagnosis Photodyn Ther*. 2019;27:433–439. doi: 10.1016/j.pdpdt.2019.06.009.
5. Ivanaga CA, Miessi DMJ, Nuernberg MAA, Claudio MM, Garcia VG, Theodoro LH. Antimicrobial photodynamic therapy (aPDT) with curcumin and LED, as an enhancement to scaling and root planing in the treatment of residual pockets in diabetic patients: A randomized and controlled split-mouth clinical trial. *Photodiagnosis Photodyn Ther*. 2019; 27:388–395. doi: 10.1016/j.pdpdt.2019.07.005.
6. Paschoal MA, Tonon CC, Spolidório DM, Bagnato VS, Giusti JS, Santos-Pinto L. Photodynamic potential of curcumin and blue LED against *Streptococcus mutans* in a planktonic culture. *Photodiagnosis Photodyn Ther*. 2013;10(3):313–9. doi: 10.1016/j.pdpdt.2013.02.002.
7. Abrahamse H, Hamblin MR. New photosensitizers for photodynamic therapy. *Biochem J*. 2016;473(4):347–64. doi: 10.1042/BJ20150942.
8. Araújo NC, Fontana CR, Bagnato VS, Gerbi ME. Photodynamic antimicrobial therapy of curcumin in biofilms and carious dentine. *Lasers Med Sci*. 2014;29(2):629–35. doi: 10.1007/s10103-013-1369-3.
9. Leite DP, Paolillo FR, Parmesano TN, Fontana CR, Bagnato VS. Effects of photodynamic therapy with blue

- light and curcumin as mouth rinse for oral disinfection: a randomized controlled trial. *Photomed Laser Surg.* 2014;32(11):627-32. doi: 10.1089/pho.2014.3805.
10. Nielsen HK, Garcia J, Væth M, Schlafer S. Comparison of riboflavin and Toluidine Blue O as photosensitizers for photoactivated disinfection on endodontic and periodontal pathogens in vitro. *PLoS One.* 2015;10(10): e0140720. doi: 10.1371/journal.pone.0140720.
 11. Brancaleon L, Moseley H. Laser and non-laser light sources for photodynamic therapy. *Lasers Med Sci.* 2002;17(3):173-86. doi: 10.1007/s101030200027.
 12. Araújo NC, Fontana CR, Gerbi ME, Bagnato VS. Overall-mouth disinfection by photodynamic therapy using curcumin. *Photomed Laser Surg.* 2012;30(2):96-101. doi: 10.1089/pho.2011.3053.
 13. Mahdi Z, Habibollah G, Mahbobeh NN, Mina ZJ, Majid Z, Nooshin A. Lethal effect of blue light-activated hydrogen peroxide, curcumin and erythrosine as potential oral photosensitizers on the viability of *Porphyromonas gingivalis* and *Fusobacterium nucleatum*. *Laser Ther.* 2015;24(2):103-11. doi: 10.5978/islsm.15-OR-09.
 14. Sreedhar A, Sarkar I, Rajan P, Pai J, Malagi S, Kamath V, et al. Comparative evaluation of the efficacy of curcumin gel with and without photo activation as an adjunct to scaling and root planing in the treatment of chronic periodontitis: A split mouth clinical and microbiological study. *J Nat Sci Biol Med.* 2015;6(Suppl 1): S102-9. doi: 10.4103/0976-9668.166100.
 15. Najafi S, Khayamzadeh M, Paknejad M, Poursepanj G, Kharazi Fard MJ, Bahador A. An in vitro comparison of antimicrobial effects of curcumin-based photodynamic therapy and chlorhexidine, on *Aggregatibacter actinomycetemcomitans*. *J Lasers Med Sci.* 2016;7(1):21-5. doi: 10.15171/jlms.2016.05.
 16. Ricci Donato HA, Pratavieira S, Grecco C, Brugnera-Júnior A, Bagnato VS, Kurachi C. Clinical comparison of two photosensitizers for oral cavity decontamination. *Photomed Laser Surg.* 2017;35(2):105-110. doi: 10.1089/pho.2016.4114.
 17. Pourhajibagher M, Chiniforush N, Monzavi A, Barikani H, Monzavi MM, Sobhani S, et al. Inhibitory effects of antimicrobial photodynamic therapy with curcumin on biofilm-associated gene expression profile of *Aggregatibacter actinomycetemcomitans*. *J Dent (Tehran).* 2018;15(3):169-177.
 18. Saitawee D, Teerakapong A, Morales NP, Jitprasertwong P, Hormdee D. Photodynamic therapy of *Curcuma longa* extract stimulated with blue light against *Aggregatibacter actinomycetemcomitans*. *Photodiagnosis Photodyn Ther.* 2018;22:101-105. doi: 10.1016/j.pdpdt.2018.03.001.
 19. Pourhajibagher M, Parker S, Chiniforush N, Bahador A. Photoexcitation triggering via semiconductor graphene quantum dots by photochemical doping with curcumin versus perio-pathogens mixed biofilms. *Photodiagnosis Photodyn Ther.* 2019;28:125-131. doi: 10.1016/j.pdpdt.2019.08.025.
 20. Mahdizade-Ari M, Pourhajibagher M, Bahador A. Changes of microbial cell survival, metabolic activity, efflux capacity, and quorum sensing ability of *Aggregatibacter actinomycetemcomitans* due to antimicrobial photodynamic therapy-induced bystander effects. *Photodiagnosis Photodyn Ther.* 2019;26:287-294. doi: 10.1016/j.pdpdt.2019.04.021.
 21. Bärenfaller V, Clausen C, Sculean A, Eick S. Effect of photoactivated disinfection using light in the blue spectrum. *J Photochem Photobiol B.* 2016;158:252-7. doi: 10.1016/j.jphotobiol.2016.03.006.
 22. Aoki A, Sasaki KM, Watanabe H, Ishikawa I. Lasers in nonsurgical periodontal therapy. *Periodontol 2000.* 2004;36:59-97. doi: 10.1111/j.1600-0757.2004.03679.x.
 23. Chiniforush N, Pourhajibagher M, Shahabi S, Kosarieh E, Bahador A. Can antimicrobial photodynamic therapy (aPDT) enhance the endodontic treatment? *J Lasers Med Sci.* 2016;7(2):76-85. doi: 10.15171/jlms.2016.14.
 24. Braun A, Dehn C, Krause F, Jepsen S. Short-term clinical effects of adjunctive antimicrobial photodynamic therapy in periodontal treatment: a randomized clinical trial. *J Clin Periodontol.* 2008;35(10):877-84. doi: 10.1111/j.1600-051X.2008.01303.x.
 25. de Oliveira RR, Schwartz-Filho HO, Novaes AB, Garlet GP, de Souza RF, Taba M, et al. Antimicrobial photodynamic therapy in the non-surgical treatment of aggressive periodontitis: cytokine profile in gingival crevicular fluid, preliminary results. *J Periodontol.* 2009;80(1):98-105. doi: 10.1902/jop.2009.070465.
 26. Barbosa FI, Araújo PV, Machado LJC, Magalhães CS, Guimarães MMM, Moreira AN. Effect of photodynamic therapy as an adjuvant to non-surgical periodontal therapy: Periodontal and metabolic evaluation in patients with type 2 diabetes mellitus. *Photodiagnosis Photodyn Ther.* 2018;22:245-250. doi: 10.1016/j.pdpdt.2018.04.013.
 27. Bechara Andere NMR, Dos Santos NCC, Araújo CF, Mathias IF, Rossato A, de Marco AC, Santamaria M Jr, Jardini MAN, Santamaria MP. Evaluation of the local effect of nonsurgical periodontal treatment with and without systemic antibiotic and photodynamic therapy in generalized aggressive periodontitis. A randomized clinical trial. *Photodiagnosis Photodyn Ther.* 2018;24:115-120. doi: 10.1016/j.pdpdt.2018.09.002.
 28. Dovigo LN, Pavarina AC, Ribeiro AP, Brunetti IL, Costa CA, Jacomassi DP, et al. Investigation of the photodynamic effects of curcumin against *Candida albicans*. *Photochem Photobiol.* 2011;87(4):895-903. doi: 10.1111/j.1751-1097.2011.00937.x.
 29. Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res.* 2001;21(4B):2895-900.
 30. Atsumi T, Tonosaki K, Fujisawa S. Comparative cytotoxicity and ROS generation by curcumin and tetrahydrocurcumin following visible-light irradiation or treatment with horseradish peroxidase. *Anticancer Res.* 2007;27(1A):363-71.
 31. Corbin F 3rd. Pathogen inactivation of blood components: current status and introduction of an approach using riboflavin as a photosensitizer. *Int J Hematol.* 2002;76 Suppl 2:253-7. doi: 10.1007/BF03165125.