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SYSTEMATIC REVIEW

Combining antimicrobial photodynamic therapy with curcumin and with methylene blue against *S. mutans*

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ABSTRACT

Antimicrobial photodynamic treatment (aPDT) is a treatment method that links a light source to a photosensitizing carrier. There is no clear standardization regarding the exact therapeutic concentration when it is combined with curcumin or methylene blue, and there is no comparison of their activities toward *S. mutans*. We aimed to assess the best composition of the combination of aPDT and curcumin and with the combination of aPDT and methylene blue in reducing the number of *S. mutans* biofilms. The searches were carried out in Pubmed, ScienceDirect, and Proquest from 2015 to April 2023; collecting in-vitro and in-vivo research. Two authors independently reviewed studies, assessed their quality and eligibility, then extracted the data. 14 articles that met the inclusion criteria were retained. The final results were then grouped into 2, showing the effectiveness for a combination of aPDT and methylene blue and of aPDT and cucumin (9 and 5 articles, respectively). Each combination has different aPDT properties. The combination of aPDT and methylene blue is effective in reducing S. mutant biofilm in 660 nm diode laser wavelength and 40 mW output power. Furthermore, aPDT combined with curcumin is effective in reducing *S. mutants* biofilm in a wavelength of 405 nm and an irradiation time of 50-150 seconds. The addition of EDTA in a combination of aPDT and curcumin could increase its effectivity.

Keywords: curcumin; medicine; methylene blue; photodynamic therapy; *S. Mutans.*

INTRODUCTION

The oral cavity is a complex and dynamic system, inhabited by more than 700 different species of bacteria. Under normal conditions, the bacterial community lives symbiotically and does not harm the host it occupies. However, environmental changes can change the balance, turning these bacteria pathogens and causing diseases in the oral cavity, such as dental caries.[1] Dental caries is a multifactorial disease, one of which is due to the role of *S.mutans.*[2] *S. mutans* are rarely found on healthy enamel, although it is frequently identified from dental plaque at carious locations.[3] Numerous virulence traits are present in *S. mutans*, such as acidogenesis, proton ATPase activity (linked to the lipid and protein components of its membrane), and acid survival.[4]

Biofilms are formed from bacterial colonies, where the process of formation and maturation of biofilms is still unknown.[5] Biofilm on the tooth surface is called dental plaque where dental plaque, which is the tenacious microbial community known as the plaque biofilm is embedded in an extracellular polysaccharide matrix and adheres to the mouth's soft or hard tissue surfaces. It is made up of both living and dead bacteria, as well as their extracellular products, and host compounds that are primarily derived from saliva.[6,7] Currently chemical therapy includes the use of antibacterial agents and flouride treatments, is required. This is done to reduce bacterial attack, change

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the biofilm, and provide prevention rather than continued caries development.[8] Due to the variety of bacterial, viral, and fungal flora living in the oral cavity and the emergence of antibiotic resistance, there have been various responses to traditional treatments, such as triple antibiotic pastes and calcium hydroxide. This had led to greater success of treatments using modern techniques for bacterial control, such as Antimicrobial Photodynamic Therapy (aPDT).[9]

Antimicrobial photodynamic treatment (aPDT) is a treatment method that combines a light source with a photosensitizing carrier. This treatment results in the generating reactive oxygen specimens (ROS) capable of naturally oxidizing atoms.[10] Light waves and the photoactive agent (PS) can react to form ROS, such as free radicals and singlet oxygen, which can cause harmful oxidative reactions on the cell wall or membrane that can kill microorganisms.[11] In the oral cavity, photodynamic treatment is generally used to treat mouth sores, such as mucositis and herpes,[12,13] and recently also used as an antimicrobial to reduce biofilm, both in microbes and in fungal infections adhering to tooth surfaces and soft tissues in the oral cavity.[14]

A photosensitizer is a basic, harmless photosensitive compound in aPDT.[15] Currently, aPDT has been combined with several types of compounds to achieve good photosensitizer quality. Methylene blue has been used as a combination treatment with aPDT to reduce biofilms of *S. mutans* in several studies. Methylene blue has low toxicity when applied to humans and, due to its lipophilic character, exhibits greater cell distribution and the ability to penetrate blood cells, therefore, it offers alternative possibilities for clinical use in aPDT.[16] In addition to the combination with methylene blue, a combination of aPDT with a natural substance, namely Curcumin, has been tried. Curcumin is a diarylheptanoid, a group of curcuminoids, a natural phenols responsible for the yellow color of turmeric.[17] Curcumin has health effects, namely as a cancer prevention agent which has calming properties, as antimicrobial and anticancer.[18]

Due to the lack of clear standardization regarding therapeutic concentrations and parameters of the best light source for the combination of aPDT with curcumin or methylene blue on S. mutans, a systematic review was carried out to find out what concentration was most effective in reducing the number of S. mutans biofilms in a combination of aPDT and curcumin or aPDT and methylene blue.

MATERIALS AND METHODS

This systematic review was conducted based on the guidelines of the Prisma Statement; Three databases (Pubmed, ScienceDirect and ProQuest) from 2015 to April 2023 were used to search articles either in in-vitro or in-vivo research. An electronic search was performed using a combination of keywords: antimicrobial photodynamic therapy OR aPDT OR Photochemotherapy" OR "Photody-namic therapy" AND CUR OR Turmeric OR Curcuma longa OR curcumin AND Methylene blue OR ME OR MB AND *S. mutans* OR mutans streptococci OR Streptococcus mutans OR streptococcus OR '*S mutans*' in all databases. Table 1 showed the search strategy. After that, duplicated articles were removed. The articles were re-selected according to the screening of title and abstract by two researchers independently. The inclusion criteria used in this examination are: (1) Articles of in-vitro or in-vivo study; (2) article was written in English; (3) Research must involve a combination of either aPDT and curcumin, or aPDT and methylene blue; (4) Studies must measure the *S. mutants* count.

All of the search results were sent to EndNote X7.3 software in where all duplicate references were then removed. Two examiners independently screened all titles and abstract for eligiblity. The full text of the included articles was then downloaded and read by two independent examiners. Articles were included in the analysis when after the full-text reading, the articles matched with the inclusion criteria and the data could be extracted. During the full-text reading,

Table 1. Keywords of Searching

Name	Synonyme
aPDT	antimicrobial photodynamic therapy OR aPDT OR Photochemotherapy" OR "Photodynamic therapy"
Curcumin	CUR OR Turmeric OR Curcuma longa OR curcumin
Methylene blue	Methylene blue OR ME OR MB
Streptococcus Mutans	S. Mutans OR mutans streptococci OR Streptococcus mutans OR streptococcus OR 'S. *mutans*'

the important data were extracted, while at the same time, the articles were critically appraised using the JBI critical appraisal checklist. In cases where differences consensus at any stage, the third's opinion was sought from the third examiner and all differences were solved by consensus. Finally, all of the data were presented narratively and discussed. Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institue (JBI) critical appraisal checklist for Randomized Controlled Trials.

RESULTS

The search was conducted in three different databases namely ScienceDirect, PubMed, and ProQuest. The initial search found 279 articles from the Science Direct database, 97 articles from the Pubmed database, and 215 articles from the Proquest database. About 479 articles were excluded due to duplication and non-compliance with the inclusion criteria during the title and abstract reading, so the total articles ended up to 112 for the full-text searching. After the full-texts were downloaded and read, another 98 obtained articles that did not meet the inclusion criteria were excluded. At the end, there were 14 articles that

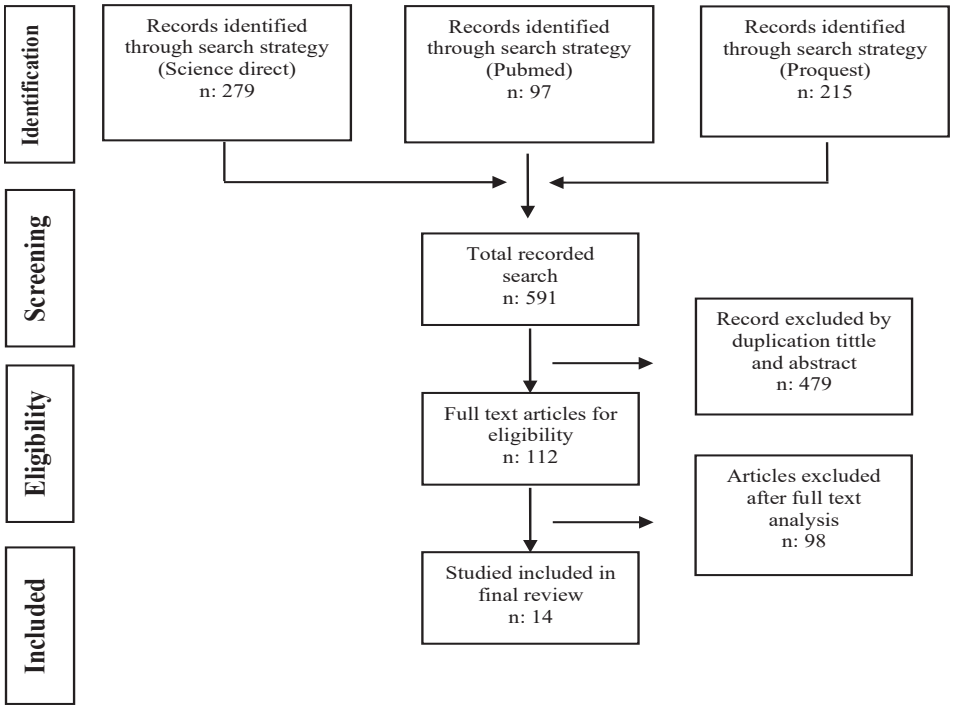

Figure 1. Flow chart of literature search

Table 2. Data extactions of aPDT with Methylene Blue articles

Authors	Study Design	Duration (min/s)	Wavelenghth (nm)	Power density (mW cm^{-2})	aPDT treatment	control	outcome	Result
Diniz et al, 2015 (19)	In Vitro	60 s	660 nm	40 mW	MB+diode laser	MB PDTlaser	*S. mutans*	The aPDT protocol (MB+ / Laser+) was effective in reducing the bacterial load of the *S. mutans* UA159 biofilm. Reduced in 81.01%
Nemezio et al, 2017 (20)	In vitro	5 min	660 nm	NA	MB+ diode laser	NaCl CHX	*S. mutans*	Compared with NaCl, the combined treatment with aPDT markedly reduced the viable bacterial counts, but less strongly than CHX
Neves et al, 2016 (21)	In Vitro	120sc	660 nm	NA	MB + diode laser	MB	*S. mutans*	Applied in the deep dentine, the number of bacteria before and after treatment did not experience a significant loss
Mocuta Bojoga et al, 2021 (22)	In vitro	NA	660 nm	50 mW	2% MB photosensitizer + LED	MB CHL-PC CHL-PC + PDT 2% CHX	*S. mutans*	The use of MB photosensitizer combined with PDT and the CHL-PC photosensitizer combined with PDT, induced a decrease in the number of bacterial colonies of S. mutans (mean±SD=4.33±1.21 and 3.67±1.21, respectively)
Furtado et al, 2020 (23)	In vitro	90 s	600 nm	NA	MB (0,005%) + low-power laser (0,1,3 and 5 min)	PBS	*S. mutans*	All aPDT groups presented a bactericidal effect by significantly decreasing the number of viable *S. mutans,* when compared with control group, without statistical differences among the different PIT periods assessed.
Méndez et al, 2018 (24)	In vitro	NA	454nm	NA	1. 100 mg/L MB + 37.5 J/cm^2 LED 2. 100 mg/L MB plus 75 J/cm^2 LED	1.100 mg/LMB alone 2. 37.5 J/cm^2 LED alone 3. 75 J/cm^2 LED alone	*S.mutans*	100 mg/L methylene blue and 75 J/cm^2 LED irradiation reduced the viability of microorganisms and the vitality of microcosm biofilms, decreasing in 23.9% mutans streptococci
Azizi et al, 2016 (25)	In vitro	60 sc	660 nm & 810nm	NA	MB+ 660nm diode laser	CHX MB IG IG+ 810 nm diode laser	*S.mutans*	after treatment with MB+aPDT; IG + aPDT; ; and CHX, *S.mutans* bacteria were completely eradicated

Authors	Study Design	Duration (min/s)	Wavelenghth (nm)	Power density (mW cm^{-2})	aPDT treatment	control	outcome	Result
Pereira Leticia Martins et al, 2020 (26)	In vitro	NA	660 nm	NA	MB+ low-power laser	Saline steril PA MB PA+MB LLL PA+PDT PA+MB+PDT	*S. mutans*	The greatest reductions in *S. mutans* growth occurred in the PDT (MB), 53.62%
Alhenaki et al, 2021 (27)	In vitro	60sc and 180sc	480nm	526 (mW/cm^2)	MB 500mg/L +diode laser	RB + diode laser PD 5ml + LED 0.12% CHX (control)	*S.mutan*	the results of MB treatment as a photosensitizer against s.mutants are still not effective in reducing the number of bacterial biofilms compared to CHX which is effective in reducing the number of bacteria

aPDT = antimicrobial photodynamic therapy; MB = Methylene Blue; LED = light emitting diode; CHX = Chlorhexidine; IG = Indocyanine Green; NA = Not available; CPM = hlorophyllin–phycocyanin mixture; PA= polyacrylic acid; CHL–PC = chlorophyllin phycocyanin mixture; PBS: Phospate buffer saline; PIT = pre irradiation time; PD = porphyrin derivative; RB = rose bengal

were retained for analysis. Details of the search flowchart were presented in Figure 1. Nine articles[19-27] measured the effectiveness for a combination of aPDT and methylene blue on s. mutans while five articles[28-32] measured the effectiveness for a combination of aPDT and curcumin on s. mutans.

The data extracted from articles of aPDT with methylene blue and aPDT with curcumin are presented in Table 2 and Table 3, respectively. In this study, a light emitting diode (LED) was used with a wavelength ranging from 405 nm to 660 nm. The effect of energy was reported in all studies. Power output, optical fiber diameter, and number of laser sessions were not discussed in any of the studies, so it was assumed that only one session was performed in each experiment. Irradiation duration was reported in all studies, ranging from 60 s to 5 min, with power density ranging from 40 to 59 Mw and energy density ranging from 10 J/cm^2 to 75.5 J/cm^2 (Table 2 and 3).

The outline of most studies features a well-structured title and summary. In addition, there is a clear introduction and rationalization of the research objectives. However, only one article discusses the scientific and statistical hypotheses. Overall, all studies provided detailed designs, statistical procedures, and detail scientific discussion.

DISCUSSION

Antimicrobial photodynamic treatment (aPDT) is a treatment method that combines a light source with a photosensitizing carrier. This treatment results in the generation of reactive oxygen specimens (ROS) capable of naturally oxidizing atoms.[10] In the oral cavity itself, PDT is generally used to treat mouth sores, such as mucositis and herpes,[12,13] and recently also used as an antimicrobial to reduce biofilm both in microbes and in fungal infections adhering to tooth surfaces and soft tissues in the oral cavity.[14] Antibacterial photodynamic therapy (aPDT) is one of the treatment options for deep dentine caries lesions, because it can reduce the bacterial load of living microorganisms in the dentine so that tooth tissue can be repaired. In addition, the infected superficial and soft

Table 3. Data extraction of aPDT with Curcumin articles

Authors	Study Design	Duration (min/s)	Wavelenghth (nm)	Power density (mW cm^{-2})	aPDT treatment	control	outcome	Result
Hwang et al, 2021 (28)	In Vitro	5 min	405 nm	59 mW	CUR+LED	Distilled water +LED Chlorella + LED Listerin+LED	*S. mutans*	the antibacterial effect of Curcuma extract+LED showed a 50% decrease S. Mutant bacteria it was higher than that of the Chlorella extract+LED
Lamarque et al, 2019 (29)	In vitro	11 min	420 nm	40 mW	CUR (+) + LED(+)	CUR(-) + LED(-) CUR (-) + LED (+) 0.06% CHX 0.12% CHX	*S. mutans*	curcumin-aPDT reduce microorganisms S,mutans after 11 min and a substantive effect of CHX, confirmed by the reduction of viable cells of specific microorganisms after 24 h
Mendez et al, 2018 (30)	In vitro	2 min	455 nm	40 mW	600 µmol/L CUR+ 37,5 J/cm^2 LED 600 µmol/L CUR+ 75 J/cm^2 LED	LED(-)+CUR(-) LED 37,5 J/cm^2 LED 75 J/cm^2 LED(-)+CUR(+)	*S. mutans*	only treatments with curcumin-EDTA-mediated aPDT were effective in reducing the vitality of intact biofilms in relation to no treatment group.
Panhóca et al, 2016 (31)	In vitro	NA	630 nm	NA	CUR+LED	CUR(-)+LED(-) CUR + NO light Photogem+LED	*S. mutans*	CUR+ led can reduce the number of S.mutan but no as good as Photegem + Led.
Merigo et al, 2020 (32)	In vitro	NA	TB= 650nm CUR= 405nm	NA	CUR + 20 J/cm^2, 30 J/cm^2 diode laser	Negative kontrol Blue diode 10 J/cm^2 Red diode 10 J/cm^2, 20 J/cm2, 30 J/cm^2 + Tluidine blue Green diode10 J/ cm^2, 20 J/cm2, 30 J/ cm^2+erythrosine	*S. mutans*	The combination of laser and the right color (Green diode effect with erythrosine) gives the result a good bactericidal effect compared to other treatments.

aPDT= antimicrobial photodynamic therapy; CUR= Curcumin; NA= Not available; LED = light emitting diode;

dentine tissue can be partially removed, so that the remaining good teeth can be preserved. aPDT may be an option for the treatment of carious lesions.[19]

Antimicrobial photodynamic therapy, or aPDT, uses a diode laser,[33] which can be combined with methylene blue. This therapy is a two-step process in which both a light source and a photosensitizer could not provide an antimicrobial effect when being used alone. The combination of aPDT with methylene blue has been used in various wavelength between 454-660 nm with different irradiation times, namely 60 sc, 90 sc, 120 sc, and 5 min.

A study by Nemezio et al[20] showed that the combination of aPDT with methylene blue can significantly reduce the number of mutant bacteria when compared to NaCl, but less significantly when compared to chlorhexidine. This finding confirms the well-known antimicrobial properties of chlorhexidine, since chlorhexidine has ability to increase the permeability of the bacteria cell membran, promoting membrane disruption and cellular death.[34] Different study of aPDT showed that with a combination of 100 mg/L methylene blue and 75 J/cm^2 LED radiation, the viability of microorganisms and the vitality of microcosm biofilms, decreasing in 23.9% of mutans streptococci.[24] Azizi et al[25] in their research compared the use of methylene blue (MB) + 660 nm diode laser with 40 mW output power to Indocyanine Green (IG) + 810 nm diode laser with 60 mW output power and chlorhexidine towards *S.mutans* bacteria count. It was found that in all of the three groups, the *S. mutants* bacteria could completely eradicated.[25] In the research conducted by Pereira et al the greatest reductions in *S. mutans* growth occurred in the aPDT combined with methylene blue.[26]

aPDT can be made by combining photodynamic therapy with curcumin, because extract of curcumin contains antibacterial, anticancer, antioxidant and anti-inflammatory effects. Apart from being a combination of aPDT therapy, curcumin extract has been used as an additional ingredient in the development of herbal cosmetic products and natural dyes.[35] The results of research conducted by Hwang et al (2021), Lamarque et al (2019) and Panhóca (2016) showed that aPDT combined with curcumin can reduce the number of *S.mutants* bacteria.[28,29,31] In Hwang et al's study, the 405 nm wavelength was used, which is relatively high in biofilms but relatively safe in the human body.[28] The results of Lamarque et al showed that aPDT combined with curcumin can reduce the amount of biofilm from *S.mutants* bacteria because e photodynamic effect can be reduced by the organic structure of carious dentin, decreasing the binding efficiency of photosensitizer to bacterial colonies and attenuating the penetration of irradiation necessary to photoactivate the dye.[29] Results of Panhóca et al's study showed that the best results were shown in the group photogem + light because antibacterial activity of curcumin is greatly enhanced by light, in dentistry a Photogem® which is a derivative of hematoporphyrin is used to treat cancer of the oral cavity and as an antimicrobial agent during aPDT.[31] The lack of photochemical stability in solutions obtained from curcumin makes its potential to generate toxic oxygen decrease due to the rapid degradation process.[36]

Research conducted by Mendez et al proves that exposure to aPDT mediated by curcumin – EDTA was effective in reducing the vitality of intact biofilms, and reduced the vitality of intact dentine caries biofilms in half the time of blue LED activation compared to curcumin alone, in addition the effect of the combination of curcumin – EDTA could decrease the vitality of the three layers equally. This suggests that EDTA enhances the effect of aPDT and favored the in-depth action of aPDT.[30] Whereas in Merigo et al's research that aPDT+ curcumin can reduce the number of *S. mutans* with different fluence, At fluence 30 J/cm^2 the bacteria decreased more than fluence 10 J/cm^2 and 20 J/cm^2 the greater the fluence, the more the number of bacteria is reduced.[32] The use of curcumin extract has been shown to reduce the number of *S. mutant* bacteria, this is in accordance with research conducted by Merigo that under light with an irradiation time of 50-150 and the bactericidal action of curcumin is effective because of its ability to diffuse rapidly throughout cells.[32] The use of a 405 nm light source and a low concentration of natural photosensitizers, can be used to develop various preventive treatments and oral care products to prevent oral diseases due to bacterial infections.[32] The disadvantage of using aPDT is that many dentists are still not confident in treating caries using this new methods, even after considerable research. Another disadvantage is that long exposure periods are required to achieve a significant inhibitory effect on microbes associated with oral disease.[37] Nevertheless, with the use of lasers, LED, and other dental

technologies, this therapy has promising future applications in the treatment of dental caries and other oral cavity conditions.

CONCLUSION

PDT combined with curcumin is effective in reducing the number of biofilms on *S. mutants* at a wavelength of 405 nm and an irradiation time of 50-150 seconds and an energy density of 30 J/ cm^2 with a result of 99.26% inhibiting S. mutants bacteria compared to other aPDT + curcumin treatments. Methylene blue with a 660 nm diode laser with 40 mW output power **completely eradicated** *S. mutans* bacteria.

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CONFLICT OF INTEREST

All authors declare that there are not any competing interests.

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