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Seyedeh Fatemeh Seyed-Javadi Limoodi
D.D.S, Tehran University of Medical Sciences, School of Dentistry, Tehran, Iran

Farshad Khosraviani
D.D.S, University of California Los Angeles, School of Dentistry, California, USA

Negar Moghaddasi
D.D.S, Shiraz University of Medical Sciences, School of Dentistry, Shiraz, Iran

Shiva Pouya
D.D.S, Tabriz University of Medical Sciences, School of Dentistry, Tabriz, Iran

Corresponding Author:
Seyedeh Fatemeh Seyed-Javadi Limoodi
D.D.S, Tehran University of Medical Sciences, School of Dentistry, Tehran, Iran

Effectiveness of photodynamic therapy with curcumin against *Candida* species: A systematic review

Seyedeh Fatemeh Seyed-Javadi Limoodi, Farshad Khosraviani, Negar Moghaddasi and Shiva Pouya

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Abstract
Introduction: In recent years, photodynamic therapy (PDT) has shown an effective role in controlling fungal infections such as oral candidiasis both in laboratory and clinical settings. Curcumin as a natural photosensitizer has antibacterial as well as antifungal effects. The aim of the present study was to evaluate the anti-*Candida* spp. effects of PDT by using curcumin.
Methods: First, the intended keywords were searched in the four following databases: Google Scholar, PubMed, Scopus and Web of Science. The titles were then merged, and the original eligible articles published by the end of 2020 were scrutinized.
Results: Out of 167 merged titles, 12 articles (*In-vitro*, *in-vivo*: mice & *G. mellonella*) met the required criteria and were included in the study. The studied *Candida* spp. were *C. albicans*, *C. dubliniensis*, *C. glabrata* and *C. tropicalis*. Concentrations of curcumin used in the studies ranged from 0.005 to 1000 µM. The light sources included LED (440-460 nm), diode laser (405, 532, 650 nm) and Xenon lamp (370-680 nm). The results of all studies showed that PDT reduced the colony count and the level of *Candida* spp. metabolism significantly. PDT efficacy was dependent on curcumin concentration, *Candida* spp., energy and wavelength of radiations, and it proved more effective in planktonic environments than biofilm environments.
Conclusion: PDT using curcumin in a concentration-dependent manner has a potent lethal effect against some *Candida* spp. and may be considered as a major or adjuvant treatment for some *Candida* infections.

Keywords: curcumin, photodynamic therapy, laser, *Candida*, fungus

1. Introduction
Fungal diseases are common treatment problems [1]. It is estimated that over one billion skin fungal infections and up to 200,000 cases of oral fungal infections may be observed around the world each year [1]. *C. albicans* and to a lesser extent *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei* cause more than 20% of fungal infections [1-4]. Diabetes, using denture, antibiotic consumption, radiation therapy, chemotherapy and immunodeficiency disorders are some of the risk factors for *Candida* spp. infection [1, 5-7]. Increased drug resistance among fungal species, the increasing prevalence of infection with non-*C. albicans* species, an increase in chronic diseases such as diabetes and immunodeficiency disorders and difficulty in managing invasive candidiasis are important challenges in treating patients with fungal infections [1, 8]. These challenges necessitate new therapeutic approaches and the production of agents that counteract with *Candida* resistance [4, 9]. Up to 9.5% of *Candida* species are resistant to fluconazole, and up to 3% are resistant to next-line drugs such as voriconazole. Unfortunately, resistance to these drugs is higher among non-*C. albicans* species [4], which adds to the existing concerns.
Photodynamic therapy (PDT) is an evolving treatment. PDT was used in the early 20th century to treat skin tumors. Over the past two decades, renewed attention to its cytotoxic effects has opened new, inexpensive, safe, non-invasive or minimally invasive therapeutic methods [10] Treatment of diseases such as periodontitis [11], healing of chronic wounds [12], accelerating the healing of oral mucositis in cancer patients undergoing chemoradiotherapy are of its therapeutic applications [12]. In addition, PDT can show a good efficacy close to that of anti-*Candida* drugs, which is a significant success [13].

PDT is based on the production of free radicals by photosensitizers (PSs). So far, various PSs have been introduced and efforts are underway to produce and strengthen their structures so that they can penetrate the cell and have a good ability to absorb light and produce free radicals [14-17]. The most common PSs used against microorganisms include methylene blue, toluidine blue and rose Bengal dyes [15].

Curcumin (Cur) has recently been introduced as a natural PS against microorganisms. Cur is the most important active polyphenol in the rhizome of Curcuma longa plant. The yellow powder of the rhizome of this plant is used as a flavor and coloring food, especially in Asian countries [18]. Cur could potentially play an effective role in controlling the pathology of some diseases and in maintaining health. Modulation of memory impairment and oxidative stress [19], anti-cancer effects, modulation of disorders related to metabolic syndrome and modulation of inflammation are among its therapeutic effects [20]. Cur reacts with proxy species at low oxygen pressures, and is capable of producing and absorbing free radicals. In addition, induction of cellular apoptosis, dimer formation and maintaining its structure in reaction with proxy species increase Cur's advantage as a PS [22, 23]. In laboratory reports Cur has shown antifungal effects [24], and its use as PDT has increased such effects.

This study aimed to investigate the role of PDT by using Cur in the control of different *Candida* species in a systematic review study. A recent review study evaluated the effect of curcumin activation by light-emitting diode (LED) irradiation on Streptococcus mutans and *Candida albicans*, and did not evaluate the other *Candida* species and light sources such as laser [23], which could change the efficacy of PDT. The present study can provide a better conclusion of the available evidence in this regard.

2. Methods

This study was designed to evaluate the published articles on the anti-*Candida* effects of PDT by using Cur. The reporting framework was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [24]. This checklist is designed for clinical trial studies but it can be used for other studies as well.

First, the following keywords were gathered based on MeSH and keywords in related articles.

(*Laser OR "Low Power Laser" OR "Low Level Laser" OR "High Power Laser" OR "Photodynamic Therapy"*) *AND* (*Candida OR "Candida albicans" OR Candidiasis OR Antifungal OR Fungus*) *AND* (*Curcumin OR Turmeric OR "Curcuma Longa"*)

The keywords were then searched in three databases: PubMed, Scopus, and Web of Science (WOS). Search results were limited to original English-language articles published by the end of 2020 using options available on the website of each database. Also, to extend the search scope, the keywords were searched in Google Scholar and the first 200 titles displayed were examined, and qualified studies were included in the study [25].

The titles were then merged into Mendeley desktop software (ver. 1.19) to remove duplicates. The remaining titles were submitted electronically to two reviewers (S.S, N.M). The reviewers reviewed the submitted articles (abstract-text) and classified them according to the study criteria.

2.1 Inclusion criteria are as follows

- Original English language articles
- Use of Cur as PS
- PDT intervention
- Using *Candida* spp. in studies

2.2 Exclusion criteria are as follows

- Lack of control groups
- Use of Cur derivatives or its modified compositions
- Flaws in the methodology or the results
- Lack of access to the full text of articles

If the two reviewers did not agree on some of the selected studies, a third reviewer (S.P) decided on them. Final articles were submitted to a fourth reviewer (F.K) to be reviewed and reported with precision.

From the articles, information including type of study, type of light source, optical wavelength, energy and power, Cur concentration, presence of other PSs, type of *Candida* species and fungicidal evaluation methods were extracted.

The results of Cur effectiveness in combination with light irradiation were reported as effective if there was a significant difference compared to the positive control group (or no significant difference with the negative control group) and ineffective if there was no significant difference with the positive control group.

To the best of our knowledge, there is no checklist to assess the quality and risk of bias in laboratory studies. Accordingly, the use of inclusion and exclusion criteria and the focus on studies' methodologies can prevent the selection of laboratory studies with high risk of bias.

3. Results

3.1 Search results

A search through the above four databases yielded 167 titles. After integrating them into Mendeley software, 118 titles remained. The titles then, were sent to the two reviewers for screening the articles based on the study criteria. 96 articles were excluded from the study, the reasons for which are shown in Figure 1. 22 titles had inclusion criteria, from which 10 articles were excluded for reasons such as adding a nanoparticle to Cur and changing its structure. Also, a clinical trial study was excluded from the study due to the lack of a control group. Finally, 12 studies were reviewed from which, information was extracted carefully. Table 1 shows a summary of the final articles.

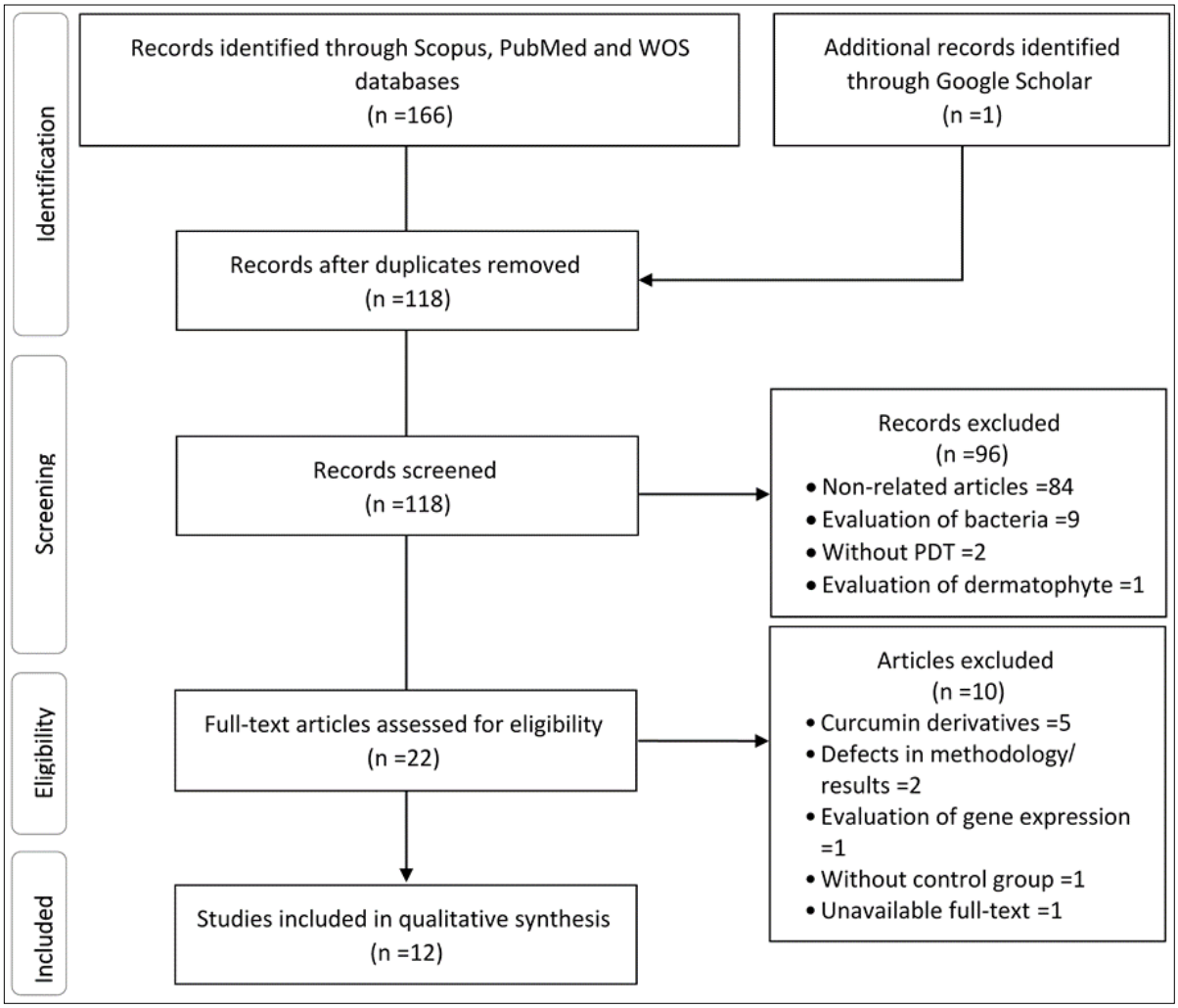

Fig 1: Articles search result

Table 1: A summary of the final studies

Author	Study type	Microorganisms	Sample	Light source	Wavelength (nm)	energy (J/cm2)	power (mW/cm2)	(µM) PS	evaluation	efficacy
Dovigo *et al*., 2011 [26]	*In-vitro*	*C. albicans*	ATCC 90028	LED	440-460	1.32-37.5	22	Cur,0.005-20	CFU/ml XTT	E
Dovigo *et al*., 2011 [27]	*In-vitro*	*C. albicans* *C. tropicalis* *C. glabrata*	clinical	LED	440-460	5.28, 18, 25.5, 37.5	22	Cur,5, 10, 20	CFU/ml XTT CV	E
Dovigo *et al*., 2013 [28]	*In-vivo*, mice	*C. albicans*	ATCC 90028	LED	440-460	37.5	89.2	Cur,20, 40, 80	CFU/ml	E
Andrade *et al*., 2013 [29]	*In-vitro*	*C. albicans* *C. glabrata* *C. dubliniensis*	ATCC 90028 ATCC 2001 CBS 7987	LED	440-460	5.28	22	Cur,5, 10, 20,30,40	CFU/ml XTT	E
Quishida *et al*., 2016 [30]	*In-vitro*	*C. albicans* *C. glabrata* *S. mutans*	ATCC 90028 ATCC 2001 ATCC 25175	LED	440-460	37.5	22	Cur,80, 100, 120	CFU/ml, XTT CV	E
Merigo *et al*., 2017 [31]	*In-vitro* *In-vivo, G. mellonella*	*C. albicans*	SC5314	Diode laser	405, 532, 650	10, 20,30	-	Cur,100 Erythrosine,100 Toluidine blue, 10	An area of growth, Survival rate	E
Al-Asmari *et al*., 2017 [32]	*In-vitro*	*Aspergillus niger* *Aspergillus flavus* *Penicillium griseofulvum*, *Penicillium chrysogenum*, *Fusarium oxysporum* *C. albicans* *Zygosaccharomyces bailii*	ATCC 6275 ATCC 9643 ATCC 48927 ATCC 1010 ATCC 62606 ATCC 10231 N ATCC 42476	Xenon lamp	370 - 680	0.24-360	500w	Cur,100-1000	CFU/ml	E
Sanita *et*	*In-vitro*	*C. dubliniensis*	CBS 7987	LED	440-460	5.28	22	Cur,5,10,20,	CFU/mL	E

al., 2018 [33]			Clinical					30, 40	XTT	
Hsieh *et al*., 2018 [34]	*In-vitro*	*C. albicans*	ATCC 90029	LED	440-460	9	22	Cur,1, 5, 10, 20, 40, 80	CFU/mL	E
da Silva *et al*., 2019 [35]	*In-vitro*	*C. albicans*	ATCC 18804	LED	440-460	67	21.1	Cur,1.5%	CFU/ mL	E
Ma *et al*., 2019 [36]	*In-vitro*	*C. albicans*	ATCC 90028 Clinical	LED	440-460	2.6, 5.4, 7.9, 10.7, 13.2	22	Cur,20, 40, 60, 80, 100	XTT	E
Rocha *et al*., 2020 [37]	*In-vitro*	E. coli MRSA *C. albicans*	ATCC 25922 ATCC 33591 ATCC 90029	LED	440-460	10.8,32.4	18	Cur,30,60	CFU/ mL	E

3.2 Type of studies
All the 12 reviewed studies were performed *In-vitro* or on animal, and no human clinical trials were observed. In addition to the culture medium, two studies evaluated the intervention on the tongue and oral mucosa of mice [28] and *G. Mellonella* larvae [31]. In the studies, the preparation and culture of *Candida* spp. were done in suspension (planktonic) and solid media (biofilm). Five studies used only biofilm to evaluate the findings [28, 30, 35–37].

3.3 Type of microorganisms and their isolation
In 11 studies, standard pre-existing laboratory species were used. In three studies, samples of *Candida* spp. were provided from the human oral mucosa including people with AIDS, lichen planus and oral candidiasis [27, 33, 36]. Six studies used only *C. albicans* to evaluate the antifungal effects of PDT [26, 28, 31, 35–37]. In addition to *C. albicans*, two studies used bacteria including Streptococcus mutans, E. coli, and Methicillin-resistant Staphylococcus aureus (MRSA) [30, 37] One study used seven fungal samples including *Candida albicans*, Aspergillus niger, Aspergillus flavus, Penicillium griseofulvum, Penicillium chrysogenum, Fusarium oxysporum and Zygosaccharomyces bailii [32]. *C. dubliniensis* was used in two studies [29, 33]. *C. glabrata* and *C. tropicalis* were other studied species of *Candida* [27, 29, 30].

3.4 Types of PS
Cur was used as PS in 12 studies. Methylene blue and erythrosine were also used in one study [31]. 10 studies used low concentrations of Cur (0.005-100 µM) and one study used concentrations of 100-1000 µM Cur [32]. In one study, Cur concentration was reported as 1.5 g / Lit [35]. Toluidine blue with a concentration of 10 µM and erythrosine with a concentration of 100 µM were used in one study [31].

3.5 Light source and radiation conditions
The LED was irradiated in ten studies with a wavelength range of 420-460nm. One study used the diode lasers with three wavelengths of 405, 532 and 650 nm [31]. One study used a Xenon lamp with a radiation spectrum of 370-680 nm [32].

In the LED group, the radiation power densities were 18, 21.1, 22 and 89 mw / cm^2, and the energy density of radiations varied from 1.32 to 37.5 J / cm^2. In the laser groups, the power density of radiation was not reported and the radiation energy densities were 10, 20 and 30 J / cm^2 [31]. In the Xenon lamp group, the radiant power was 500W, and its radiation energy densities were 24.5 and 73.2 J / cm^2 [32].

3.6 Investigation of anti-*Candida* effects
Colony count (CFU / mL) was used in nine studies; assessment of the level of cellular metabolism by the XTT assay was done in six studies, and growth inhibition zone in the biofilm was used in one study [31]. Also, two studies used crystal violet staining and optical spectrometry to investigate the lethal effect as well as the reduction of microorganisms' attachment to the wall of the culture dishes [27, 30]. Five studies simultaneously used colony count and examined the level of cell metabolism by the XTT assay [26, 27, 29, 30, 33].

3.7 Effectiveness
In all studies, PDT, compared to the positive control group, showed a significant result on reducing colony counts, metabolism and attachment of *Candida* spp., other fungal species and bacteria in both biofilm and planktonic environments. In nine studies, in some settings, the reduction of *C. albicans*, *C. dubliniensis* and *C. tropicalis* reached 100% which occurred mainly in the planktonic environment [26, 27, 29–32, 34]. *C. glabrata* showed less sensitivity to PDT and their removal was incomplete.

All three light sources interacted well with Cur and their radiation wavelengths were shown effective. In a histological study, partial elimination of *Candida albicans* and modulation of inflammation were seen in mice tongue [28]. In addition, PDT increased the survival of the infected larvae with *C. albicans* [31].

In the studies, in general, a significant and direct relationship between fungicidal effect and Cur concentration, radiation energy and contact time with Cur before irradiation was recorded. The following is a summary of the reviewed studies. In their three studies, Dovigo *et al*. investigated the optimal doses of Cur on different laboratory and clinical species of *Candida*. In addition, investigations were made on the effect of PDT with the help of Cur on the treatment of oral candidiasis of mice [26-28].

First, they investigated the effect of 0-20 µM Cur with a maximum energy of 37.5 J / cm^2 and a contact time with Cur of 0-20 minutes on the *C. albicans*. Concentrations of 5, 10, 20 µM had the most lethal effect. At a concentration of 20 µM and energy of 5.28 J/cm^2 (4 minutes irradiation) complete lethality was achieved, and the increase of irradiation time had no significant effect. In the biofilm environment, based on the results of planktonic environment, concentrations of 5, 10, 20, 30, 40 µM, energy of 5.28 J/cm^2 and contact time of 0-20 minutes were used. The contact time of 1 to 20 minutes before irradiation was able to reduce the colony count. The increase of contact time showed a better effect in lethality. The best results were obtained with 20 minutes of contact time, 20 µM Cur and a radiation intensity of 5.28 J / cm^2 [26].

In another study of theirs, 20 µM Cur among concentrations of 5, 10, 20, and 80 µM and a radiant energy of 5.28 and 18 J / cm^2 among radiation energies of 5.28, 18, 25.5 and 37.5 J / cm^2 showed the best results on the reduction of *C. albicans*, *C. tropicalis* and *C. glabrata* colonies in the planktonic environment. In the planktonic environment, a concentration of 20 µM and a minimum energy of 18 J / cm^2 completely killed *C. tropicalis*. Not all of the above concentrations and energies had a complete lethal effect on *C. glabrata* in the

planktonic medium. Cur by concentrations of 20, 30 and 40 µM were evaluated in a biofilm medium. After biofilm formation, the above concentrations were contacted with the culture medium for 20 minutes, and then an LED with an energy of 5.28 and 18 J / cm^2 was radiated. The reduction of metabolism in biofilm for *C. albicans*, *C. tropicalis* and *C. glabrata* was 85.3%, 80.1% and 42% respectively. Also, the reduction rates of cell adhesion to the plastic dish wall for the above *Candida* spp. were 53.2%, 69.1% and 64.1% respectively [27].

Dovigo *et al*. reported the effectiveness of PDT with Cur in the mice model as well. Oral mucosa of the mice was infected with *C. albicans* under immunosuppressive conditions, and Cur was exposed to oral mucosa and tongue at concentrations of 20, 40, and 80 µM, and after 20 minutes, an LED light was radiated. Radiation continued for 7 minutes at a total dose of 37.5 J / cm^2. All PDT settings significantly reduced *C. albicans*' colony. There were dose-dependent effects among which 80 µM showed the best effect [28].

Andrade *et al*. evaluated Cur pre-irradiation contact times (1, 5, 10, and 20 min) in planktonic and biofilm media for *C. albicans*, *C. glabrata*, and dubliniensis. One minute contact at 20 µM Cur completely reduced *C. dubliniensis*, however, it reduced *C. albicans* and *C. glabrata* by about 85%. Also, in the planktonic environment, all species were completely inactivated by PDT with time contacts of 5, 10 and 20 min and at a concentration of 20 µM and no significant difference was observed between the contact times before the above irradiation. For biofilm, concentrations were of 10, 20, 30 and 40 µM, and irradiation times were 4 and 8 minutes, and contact times before irradiation were 1, 5, 10 and 20 minutes. In the biofilm, both the concentration and pre-irradiation times acted independently on lethality. A concentration of 40 µM and a time of 20 minutes had the most lethal effect on the species. Radiation or Cur alone did not prove effective [29].

Quishida *et al*. analyzed the effect of PDT on the biofilms of *C. albicans*, *C. glabrata* and Streptococcus mutans 24 or 48 hours after biofilm formation. They used concentrations of 80, 100 and 120 µM of Cur. In the first 24 hours, *C. albicans* showed a significant response to PDT with all Cur concentrations without significant differences. In the measurement after 48 hours, only PDT with 120 µM Cur had a significant efficacy on *C. albicans*. In the first 24 hours, Cur of 100 and 120 µM were deadly for the *C. albicans* alone, but these concentrations were not ineffective after 48 hours. All concentrations of PDT at all times showed a significant inhibitory effect for *C. glabrata* and S. mutans [30].

Merigo *et al*. had a different study. They examined different wavelengths of diode laser and three types of PS of 100 µM Erythrosine, 10 µM toluidine blue, and 100 µM curcumin on *C. albicans* in *G. mellonella* larvae and *In-vitro* settings. The wavelengths used were 405, 532 and 650 nm and the radiation energies were 10, 20 and 30 J / cm^2. Without PS there was no lethal effect in both solid and suspension media. Cur, toluidine blue and erythrosine had the best effect in the suspension, respectively. Only PDT with Cur showed 100% lethal effect, which was seen in all radiation energies. The highest degree of inhibition was observed at 405 nm and the use of Cur at any concentration. None of the PSs had a lethal effect on larvae and were safe. PDT significantly increased larvae survival with all PSs [31].

In the study of Alasmari *et al*. Cur contact with the environment was done 10-30 minutes before or just before the Xenon lamp irradiation on a variety of fungi. Cur concentration of 100-1000 µM and radiant energies of 0.24, 48, 72 and 96 J / cm^2 were used in the suspension medium. The best response was obtained at a concentration of 600-1000 µM Cur, energy of 72 and 96 J / cm^2 and an irradiation time of 6 to 8 minutes. All doses and energies were effective on *C. albicans* and had 100% lethality. In biofilm, Cur at 800 µM and 96, 240 and 360 J / cm^2 were able to completely inhibit *C. albicans*. The time of exposure to curcumin before irradiation did not affect the lethality significantly [32].

Sanitá *et al*. evaluated PDT on *C. dubliniensis*. Samples were obtained from HIV-infected individuals as well as standard laboratory samples. Cur concentrations included 20, 30, and 40 µM, the contact time was 20 min, and radiation energy was 5.28 J / cm^2. Concentration of 20 µM in the planktonic environment completely inhibited *C. dubliniensis*. In the biofilm environment, PDT had a significant inhibitory effect at all three concentrations. 30 and 40 µM Cur alone without radiation also reduced the viability. In the planktonic medium, contact at 5 and 20 minutes produced similar light absorption, but in biofilm, at 5 minutes, only some parts of the culture medium began to absorb light [33].

Hsieh *et al*. investigated the effect of PDT or fluconazole or their combination on *C. albicans*. Cur concentrations in this study were 1, 5, 10, 20, 40 and 80 µM; contact time was 20 minutes, and radiation energy was 9 J / cm^2. In the planktonic environment, concentrations of 1 µM and 9 J / cm^2 had a relative lethal effect, and a concentration of 5 µM had complete lethality. In the planktonic environment fluconazole caused a significant decrease in *C. albicans* but in culture medium this decrease was not significant. PDT effectively reduced *C. albicans* in biofilm, and when combined with fluconazole, better significant results were obtained. Within 48 hours, the combination of PDT and fluconazole reduced the colony count to 5%, while fluconazole alone reduced the colony count to 20% [34].

Da Silva *et al*. examined PDT on bovine rib specimens infected with *C. albicans*. PDT showed a significant lethal effect compared to Cur or light alone and the control group. Cur or light alone was not significantly different from the positive control group [35].

Ma *et al*. examined PDT on *C. albicans* extracted from oral mucosa of AIDS and lichen planus patients as well as standard laboratory samples. The effectiveness of PDT on the standard sample groups was higher than that of lichen planus and AIDS patients (90.9%, 86.7% and 66.4%). Also, a concentration-dependent effect was observed, and the concentration of 60 µM was optimal [36].

Rocha *et al*. evaluated the efficacy of mouthwash containing 30 and 60 µM Cur with PDT on *C. albicans*, MRCA and E. coli biofilms. Settings included 10 minutes of irradiation - 10.8 J / cm^2 and 30 minutes of irradiation-32.4 J / cm^2. In the findings, 60 µM Cur -30 minutes of irradiation caused 89.4% reduction in *C. albicans* colony. Cur with a concentration of 30 µM decreased the MRCA depending on the irradiation time. For E. coli, the result was similar to MRCA, and the colony growth was reduced by almost 100%, but no time-dependent effect was observed [37].

4. Discussion

The findings of twelve reviewed articles showed that Cur in combination with light radiation with three sources of LED, diode laser and Xenon lamp played an effective role in reducing *Candida* spp. in both *in-vivo* and *In-vitro* models, and no placebo effect was observed.

The mechanism(s) of PDT and its cellular effects are not understood completely. The production of reactive oxygen

species (ROS) as a cellular-damaging agent may be the mechanism justifying the effect of PDT [27]. The decrease in the metabolism of *Candida* spp. after PDT in the reviewed studies can be caused by a series of damage to the cell wall, the cell membrane and the genetic content due to ROS [26, 36, 38, 39] as well as cell membrane damage due to Cur toxicity [40].

The cell wall of the fungus reduces its permeability and increases cell strength and cell attachment. Cell wall is the first barrier to Cur penetration into the fungus cell [41], and the interaction of Cur with the cell wall can be the first site of PDT damage.

In the reviewed articles PDT was used with 0.005-1000 µM curcumin and its antifungal results was dependent on Cur concentration [26-28, 30, 32-34, 36, 37]. It seems that in the suspension medium the minimum effective concentration of Cur is 5 to 20 µM and in the biofilm, the 20 µM and more appropriately the 30-40 µM concentrations have a better ability to reduce *Candida* spp. [26-28, 33, 34]. In addition to Cur concentration, three factors including *Candida* species, wavelength and radiant energy also affect the results of PDT. In four studies, PDT had a 100% reducing effect on *C. albicans*, *C. dubliniensis*, and *C. tropicalis* [27, 29, 31, 32], but this effect was not complete on *C. glabrata* [27, 29]. Although *C. glabrata* has more resistance than *C. albicans* in the clinic [42], but the present finding could be a bias because in other studies, for *C. glabrata* the minimum inhibitory concentration of Cur was higher than *C. albicans* and *C. tropicalis* [43, 44], and with increasing the concentration of Cur during PDT, its relative resistance may decrease [43, 44]. Samples collected in the clinic may be more resistant to PDT than the pre-existing standard *Candida* spp. [36]. Various standard species had also been used in studies that may affect their sensitivity to PDT.

In some of the reviewed studies, the increase in irradiation time or energy was mostly associated with the fungicidal effects [26, 27, 32, 36, 37]. In the biofilm, the radiation energy of 18-37.5 J / cm^2 seems to be effective, although a lower radiation energy is required in the suspension medium. Also, the effect of curcumin concentration can be more important than irradiation time or energy [26, 29].

In the studies, the biofilm had a weaker response to PDT than the suspension medium. Due to the greater thickness of the biofilm, there are two items that can maintain the effect of PDT relative to the suspension medium. The first is an increase in the concentration of Cur. And the second is the contact time of Cur with the biofilm before irradiation. In the latter case, the contact time provides an opportunity for Cur to penetrate into the deeper layers. According to the results, the Cur contact time, at least 5 minutes for the suspension medium and at least 20 minutes for the biofilm medium, as seen in the clinic, is the ideal time for the anti-*Candida* effects of PDT [29].

Cur has an absorption spectrum of 270 to 590 nm, and ideally, an absorption spectrum of 410 to 450 [32, 39]. This spectrum is clearly existent in the wavelength of LED lamp (440-460nm), Xenon lamp (370-680nm) and also the wavelength of 405nm diode laser compared to the other two wavelengths (532, 650nm) in the study of Merigo *et al*. [31]. Therefore, the use of light sources corresponding to the maximum absorption wavelength of Cur can bring about more successful results. Unlike LED and Xenon lamps, lasers produce photons of the same phase, energy, and direction. In other PDT studies with LED or laser, similar results have been shown to reduce bacterial [45, 46] and fungal colonies [47]. It seems that the type of PS and radiation setting are more important than the type of light sources according to the PS absorption spectrum. Lasers with and without PDT have shown different antifungal effects. In the study of Najafi *et al*. 940 nm diode laser radiation alone had an increasing or neutral effect on *C. albicans* colony [48]. In the study of Wiench *et al*., the 635 nm diode laser alone is ineffective but PDT with toluidine blue significantly reduces all three species of *C. albicans*, *C. glabrata*, and *C. krusei* [49]. In the present reviewed study, three radiation wavelengths of 650, 405 and 532 nm of diode laser and LED alone, generally had no effect, but in combination with Cur (superior result), erythrosine and toluidine blue, it showed a fungicidal effect [28, 30-32] which is similar to findings of the other studies [43, 50-52].

In a reviewed study, the effect of fluconazole on biofilm was less than that of PDT, and the combination of the two increased the antifungal effect [34]. As in other studies, Cur had a weaker effect on *Candida* spp. than azoles, nystatin and amphotericin B [50, 52-54]. Cur in combination with fluconazole and amphotericin B [44, 50] reduces the MIC of fluconazole and amphotericin B and enhances their effectiveness [34, 44]. Cur also can sensitize fluconazole-resistant *C. albicans* species [53] which adds to its advantage as a PS.

In summary, the findings of the reviewed articles showed that Cur as PS could play a fungicidal role after light irradiation on *Candida* spp., and the results generally depend on the concentration of Cur, the type of *Candida* spp. and the radiation wavelength. Further studies are needed to achieve the ideal radiation settings, especially Cur-mediated laser radiation, as well as clinical effects. To the best of our knowledge, Cur is a safe substance in the usual dosage [55, 56], and its topical administration also increases its safety due to minimizing systemic effects.

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6. Conflict of interest

The authors declare that they have no conflict of interest.

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