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Review

Curcumin-mediated Photodynamic Therapy for the treatment of oral infections—A review

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ABSTRACT

Background: Recent evidences show the promising applications of Curcumin (CUR) against different diseases, including some of the main oral pathologies. The objective of this review paper was to catalog articles that investigated the photodynamic effect of CUR for oral diseases in the last 15 years.
Methods: The establishment of defined criteria for data collection was proposed and a total of 173 articles were identified, but only 26 were eligible for full text reading. Their main findings were critically reviewed to provide a state-of-the-art overview of the use of CUR in Dentistry.
Results: Antimicrobial potential of CUR was the subject of the majority of the articles. CUR showed great potential for photodynamic action against oral bacteria, fungi, and strains resistant to conventional drugs. Some authors indicated the efficacy of CUR-mediated Photodynamic Therapy to reduce tumor cells while others observed low cytotoxicity in mammalian cells and healthy oral mucosa. However, CUR solubility and stability is still a problem for the photodynamic technique, and to overcome these drawbacks, biocompatible vehicles need to be better explored.
Conclusions: Investigations have used different CUR concentrations and formulations, as well as different light parameters. This fact, together with the lack of in vivo studies, clearly shows that clinical protocols have not been established yet. Investigations are necessary in order to establish the best concentrations and safe vehicles to be used for this technique.

1. Introduction

The combination of chemical substances and light is attributed to Oscar Raab in 1900, which accidentally promoted protozoan killing after a photo biological reaction that was later found to be an oxygen-dependent phenomenon [1]. However, investigations on the antimicrobial efficacy of the so-called 'photodynamic therapy' progressively decreased with the advent of antibiotics in 1928.

The focus of Photodynamic Therapy (PDT) has been on the development of effective protocols for cancer management. Photodynamic reaction is based on the combination of a drug, known as a photosensitizer (PS) and the delivery of an appropriate wavelength of light to excite the PS molecule [2]. Next, the PS absorbs photons and induces a series of reactions involving the formation of radicals and reactive oxygen species (ROS). Nowadays, PDT has been recognized as an effective treatment for various localized premalignant conditions and solid tumors [3,4]. In addition, the extension of PDT for the treatment of various non-oncological diseases has been the goal of several investigations.

More recently, growing antibiotic resistance has demanded the reassessment of antimicrobial PDT, particularly for superficial infections wherein the contact with light is facilitated [5]. In this scenario, numerous investigations started to study PDT against microorganisms (MOs) [6–15], and suggested this therapy in cases of microbial resistance or in association with the existing drugs to enhance its effectiveness [16]. Photodynamic inactivation of microorganisms is also known as Photodynamic Antimicrobial Chemotherapy (PACT) [5] or Photodynamic Inactivation (PDI) [17]. Since the ROS can react with non-specific targets, PDI carries several advantages over conventional antibiotics and antifungals, for example, few undesired side effects and little likelihood of promoting the development of resistance by microorganisms [18].

The literature reports the existence of synthetic and natural pigments that can be used as photosensitizers (PS) for PDT and PDI [5,8,19–23]. Despite the higher stability present by the synthetic dyes, natural compounds have been largely studied and accepted, mainly because they are less prone to collateral effects and drug interactions [7–13,24–27]. Curcumin (CUR) is a phenolic compound, member of the

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curcuminoid family, which can be extracted from the rhizomes of the *Curcuma longa*. CUR has showed great potential for use in medicine due to its bioactive properties such as the fact of having anti-inflammatory, antiseptic, anti-viral and anti-tumor effects [28–36]. Additionally, other studies have reported that CUR acts as a potential anti-neuroinflammatory agent benefiting patients diagnosed with Alzheimer, Multiple Sclerosis and Dementia caused by HIV [37]. CUR has also shown great potential as a PS because of its ability to absorb blue light [8,10,25,38–42]. Recently, a growing body of evidence shows the promising applications of CUR against different diseases, including some of the main oral pathologies [8,13,24,25].

The primary objective of the present article was to catalog papers that investigated the use of CUR-mediated PDI for oral infections in the last years. Consequently, their main findings were critically reviewed to provide a state-of-the-art overview of the use of CUR-mediated PDI in Dentistry.

2. Materials and methods

2.1. Eligibility criteria and search strategy

MEDLINE/Pubmed (National Library of Medicine, Maryland) and Elsevier's Scopus databases were searched from 2000 to 2016 using the following terms in different combinations: 'Curcumin', 'Dentistry', 'Photodynamic Therapy'. The 'exact term' was not used in the search, being accept the terms: Photodynamic Inactivation, Photochemotherapy, Antimicrobial Photodynamic Therapy, Photodynamic Antimicrobial Chemotherapy and Photo-activated Disinfection. The eligibility criteria were comprised of the following: (1) full texts available for analysis; (2) original articles (in vitro, in situ, and in vivo), and case reports; (3) studies written in Portuguese, English and Spanish; (4) studies published between January 2000 and February 2016; (5) articles that studied head and neck cancers were accepted; (6) literature reviews were also accepted in order to identify any articles that could have been missed (reference lists were hand search). A total of 173 articles were identified, being 125 using the Scopus database. Elimination of duplicates resulted in 37 articles for analysis. Only 26 were eligible for full text reading and therefore were included in the present review. Data from the 26 selected articles are summarized in Table 1. Most articles were designated to evaluate the antimicrobial efficacy of PDI, followed by investigations of new CUR formulations, cancer studies, and cytotoxicity.

3. Results

3.1. Antimicrobial efficacy of CUR-mediated PDI

Antimicrobial potential of CUR-mediated PDI was the subject of the majority of the articles found in the present review. Table 2 summarizes the species that has been evaluated in the antimicrobial investigations, most of them related to oral diseases.

Several investigations have evaluated the antimicrobial effect against oral bacteria [9–15,24,43,44], fungi [7,8,25] and strains resistant to conventional drugs [6]. Some studies have assessed the PDI efficacy in pathogens that can also be related with systemic conditions such as *Enterococcus faecalis* (Ef) [42,45–50] and *Escherichia coli* (Ec) [45–47,49].

Table 2
Summary of the microorganisms evaluated and the frequency that has been studied in the selected papers.

Target Cell	f	(%)
Streptococcus mutans	6	23.07
Lactobacillus	3	11.53
Candida spp.	4	15.38
Methicillin-resistant *Staphylococcus aureus*	1	3.84
Susceptible *Staphylococcus aureus*	1	3.84
In natura (saliva and dental plaque)	4	15.38
Enterococcus faecalis	6	26.92
Escherichia coli	4	15.38

Table 3
Relation between the selected papers and the type of photosensitizer used.

Photosensitizers	n	(%)
CUR	15	57.69
CUR salt	10	42.30
Unspecified	1	3.84
Total	**26**	**100.00**

In general, CUR-mediated PDI was effective in reducing the viability of several species. Most in vitro tests (86.36%) were conducted using planktonic cultures of the microorganisms [6–8,10,12,13,15,41,43–49], followed by investigations on single-species [6–8,42,43,48,50] and multi-species [11] biofilms. Additionally, one animal study [25] and three clinical trials were found [9,14,24].

CUR protocols vary widely among studies, which possibly explain the different results observed in some cases. CUR concentrations ranged from 0.005 to 8000 μM and the use of a 'pure' CUR (57.69% of articles) was described [6–8,12,15,25,41–44,48,51] as well as a mixture of curcuminoids (42.3% of articles), including CUR, demethoxy-CUR and bisdemethoxy-CUR [9–11,13,14,24,45–47,49]. In addition, it is important to inform that only one study did not mention the type of CUR applied [50] (Table 3). Several investigations show that CUR have great oxidative properties, low molecular weight, and high capability of light absorption and has great potential to be used as a photosensitizing drug for PDI.

3.2. Candida species

The increasing emergence of antifungal resistance has resulted in a growing interest in the antimicrobial effects of CUR-mediated PDI against *Candida* spp. Results from in vitro investigations showed that a reference strain of *Candida albicans*, in planktonic form, was completely inactivated after using 20 μM of CUR with 5.28 J/cm^2 of light [7], while clinical isolates of the same species, as well as *Candida tropicalis* strains, required further illumination (18 J/cm^2) to achieve similar results [8]. The same CUR concentration was not able to inactivate the planktonic suspensions of *Candida glabrata*, but a significant reduction of yeast viability was reported [8]. It is interesting to note that *C. glabrata* is known to be inherently less sensitive to fluconazole and other antifungal drugs [52,53]. When in vitro biofilms were used, CUR concentrations ranging from 20 to 40 uM promoted more than 70%

Table 1
Number of cataloged papers and their percentages (%) versus the main aborded themes.

	Cancer	Cell Citotoxicity (CC)	Microorganisms (MO)	MO and CC	MO and Formulations	TOTAL
n	3	1	15	3	4	**26**
(%)	11.54	3.85	57.69	11.54	15.38	**100.00**

reduction of cell metabolism [8].

The importance of the pre-illumination time (PIT) was assessed by Andrade et al. [6]. The authors showed that different incubation times (1, 5, 10 and 20 min) of planktonic cells with CUR had no influence in PDI efficacy against the *Candida* species. This may suggest that CUR binds rapidly to yeast cells or that the photodynamic effect was due to the free CUR in the surrounding medium. On the other hand, the PDI effect on biofilms showed dependence on PIT and the best results were obtained using 20 min of incubation with 40 μM of CUR [6]. The contradictory result for biofilms was probably caused by the difficulty of the CUR to penetrate the different layers of cells within the biofilm.

The PDI mechanism action against *C. albicans* is not fully understood. However, results from a recent investigation suggested that PDI promoted permanent DNA damage in *Candida* cells, which need to be further investigated [54]. There is also a lack of clinical investigations using CUR-mediated PDI to eliminate the *Candida* species. Dovigo et al. [25] assessed one protocol (80 μM CUR + 37.5 J/cm^2) in a murine model of oral candidiasis and reported that PDI promoted a reduction of 4 logs on *C. albicans* viability, indicating the potential of this treatment to overcome antifungal resistance. However, further investigations are required to establish the clinical efficacy and safety of the therapy.

3.3. Streptococcus mutans

Streptococcus mutans is the main etiological agent associated with the pathogenesis of dental caries [55]. It is the pioneer species in plaque-biofilm formation and the polysaccharides found in the biofilm matrix are recognized as the essential virulence factors associated with caries [56]. The superficial penetration of blue light into tissues has pointed out CUR as a suitable PS for teeth decontamination. Different PDI protocols were effective in reducing the viability of planktonic cultures of *S. mutans*. When the pure CUR was tested, concentrations from 0.75 to 60 μM associated with short-term illumination (12.2 s and 2 min) promoted reduction in cell viability [12,15,43]. A mixture of curcuminoids (MCUR) also promoted photodynamic effects on planktonic cultures of *S. mutans* [13].

Multi species biofilms comprised of *S. mutans* and *Lactobacillus* strains were less susceptible to PDI mediated by MCUR when compared to single *S. mutans* biofilms. The use of 0.75 and 1.5 g/L promoted a reduction of 54 and 91% on biofilms viability while the decrease in single species had reached 100% [11]. In addition, a 99% reduction of these pathogens in saliva was observed [9]. Dentin carious lesions were also exposed to PDI mediated by 3 g/L of the same MCUR and a reduction of 69.4% on the microbial content was reported [11].

In order to bring this new approach close to the daily routine, Leite et al. [24] evaluated the effects of PDI mediated by MCUR (30 mg/L + 200 J/cm^2) on oral disinfection. Results from this clinical trial showed a reduction of 1 log in microbial viability after 2 h of the disinfection protocol. On the other hand, Paschoal et al. [14] evaluated the MCUR-mediated PDI (1.5 mg/mL; 96 J/cm^2) to reduce plaque accumulation in adolescents during orthodontic treatment and found that PDI using the parameters described above were not effective. The different outcomes might have occurred due to the different protocols used in the investigations. Leite et al. [24] used a MCUR 20 times less concentrated than Paschoal et al. [14], and this fact might facilitate the drug diffusion and the light penetration in the target cells, increasing the photosensitization effect [35]. In addition, the fluence used by Leite et al. [24] was almost twice superior, which could promote more ROS formation [57–59]. Another important point is the fact that Leite et al. [24] evaluated the antimicrobial efficacy on planktonic cells in saliva, while Paschoal et al. [14] did it directly on the dental plaque, which is known to be less susceptible to therapies because the extracellular matrix hinders the drug's diffusion into the biofilm [60].

Pure CUR has not been investigated in clinical trials until this date, so there is still no adequate evidence to conclude on the efficacy of CUR-mediated PDI for dental biofilm control. Future studies should investigate the CUR effects and its mechanism of action against dental plaque, including the use of in situ models in order to establish an effective protocol.

3.4. Enterococcus faecalis

Although *Enterococcus faecalis* mainly colonize the gastrointestinal tract, the species can also be found in root canals of teeth and it has been frequently related to unsuccessful endodontic treatment [61,62]. *E. faecalis* resistance to conventional antimicrobial agents has been reported [63,64], and the PDI efficacy has been studied by many authors in order to find a feasible protocol for viability reduction [42,45–50].

Pilegi et al. [48] assessed CUR-mediated PDI (5 μM; 450 mW/cm^2; 4 min; PIT of 30 min) efficacy against *E. faecalis* and observed a viability reduction of 7 logs in planktonic cultures compared with the negative control group. However, for biofilm cultures, 10 μM of CUR was necessary to achieve total reduction, confirming that microorganisms in a biofilm form can hinder the photosensitizer diffusion through the extracellular matrix and cells [60]. Neelakantan et al. [50] also observed a high rate of dead cells from biofilms formed in root canals, although the authors have used a different PDI protocol (2.5 mg/mL; 1200 mW/cm^2; 4 min) and PIT was not reported. On the other hand, da Frota et al. [42] obtained less viability reduction in root canal biofilm (≈2 log), concluding that their PDI protocol (20 μM; 100 mW/cm^2; 5 min) was not effective for *E. faecalis* inactivation. This difference possibly exists due to the higher PIT and light fluence used by Pilegi et al. [48] and Da frota et al. [42]. It is important to highlight that the results presented by Pilegi et al. [48] are interesting since several authors mention that microorganisms in the stationary phase are characterized to be less susceptible to any therapy [65–67].

Other investigations also assessed PDI efficacy against planktonic cultures such as those of Wikene [49] and Hegge et al. [45,46]. Photokilling efficacy of CUR in different formulations was tested and high viability reduction was observed, ranging from a drop of 4 logs [49] to complete microorganism inactivation [46]. All studies used 10 min of PIT [45,46,49] and the results showed favorable outcomes for reducing *E. faecalis* viability. Among these studies, two of them presented protocols that promoted total inactivation of the suspension culture when compared to the control groups [45,46]. The authors used CUR in different formulations such as alginate discs (6 mg of CUR/disc) [45] and 10 μM of CUR in 1% M-β-CD (Methyl –cyclodextrin derivate; Cavasol^R W7) [46]. The LED light fluences were also distinct, being 29.0 J/cm^2 [45] and 4.8 J/cm^2 [46]. Thus, it is possible that besides the fact that they used different PDI protocols, the distinct formulations of CUR might have good potential for *E. faecalis* elimination.

3.5. Escherichia coli

Escherichia coli can be found in root canals of teeth after unsuccessful endodontic treatment, becoming a microorganism of dental interest which, according to the present revision, was evaluated in 4 different studies [45–47,49]. The protocol that seems to be most effective was the one tested by Hegge et al. [47] (lyophilizate CUR at 25 μM; 14 J/cm^2 of blue LED light), since it promoted complete inactivation of *E. coli* suspension when a fresh solution of CUR was used. Another promising PDI protocol to reduce *E. coli* viability in planktonic culture (CUR at 10 μM in 0.01% M-β-CD and in 1% of ethanol; PIT 30 min; 29 J/cm^2), provided only 0.01% of bacterial survival [46]. The other protocols promoted viability reduction of 81% (10 μM CUR in alginate discs of PEG 400 associated; PIT 30 min; 29 J/cm^2) [45] and 6 logs (5 μM CUR in 1% ethanol; PIT 30 min; 32 J/cm^2) [49] when compared with their respective control groups.

Gram negative bacteria has more mechanisms to defend itself against antimicrobial agents than gram positive bacteria [68], but in general, all studies that evaluated the efficacy of CUR-mediated PDI against *E. coli* obtained pronounced results. It is possible that the

promising results showed by the authors occurred because the PDI was performed on planktonic cells [60], and due to the CUR photosensitizer used, a hydrophobic compound that has affinity to other hydrophobic molecules, such as the lipopolysaccharides present in the cell wall [69], facilitating the drug diffusion inside the cells. In addition, the differences observed in those results may have occurred because of the different new excipients tested in order to make a formulation with better stability.

3.6. Lactobacillus ssp. and Staphylococcus aureus

Species of *Lactobacillus* are able to produce acids, grow and survive in acidic environments [70,71]. Due to this ability, *Lactobacillus* ssp. have been identified in carious lesions by several authors [72–75]. Thus, some studies evaluated its susceptibility to the CUR-mediated PDI and the results presented by these authors were contradictory. Araujo et al. [9] observed that the tested protocol (1.5 g/L; 5.7 J/cm^2) promoted low antimicrobial activity against *Lactobacillus* (37.6%) when microorganisms grew in single-species suspensions. On the other hand, Bulit et al. [44] observed that *Lactobacillus* suspensions were susceptible to PDI (400 μmol/L; 4 min of irradiation) since their viability was near "zero" [44] after treatment. Although both studies have evaluated *Lactobacillus* on planktonic cultures, the difference between them was evident, which was probably due to the distinct protocol used. While Araujo et al. [10] used 5 min of PIT, Bulit et al. [44] used 15 min and this fact might influence the PDI response, since the higher the PIT, the longer that the CUR stays in direct contact with the microorganisms, promoting elevated CUR penetration inside the cells. On the other hand, Bulit et al. [44] used a less concentrated CUR, which could facilitate its penetration in the target cells [35]. Another important point that could explain the distinct results is the microorganism evaluated, although the authors evaluated the same genus, Bulit et al. [44] did not specify the species utilized, and different species might respond differently to the PDI. Thus, due to the distinct results presented, it is important to highlight that there is still no adequate evidence to conclude the efficacy of CUR-mediated PDI for *Lactobacillus* viability reduction, justifying more investigations in this area.

Regarding resistant *Staphylococcus aureus*, the results showed total inactivation for the MRSA (methicillin resistant *Staphylococcus aureus*) and MSSA (methicillin susceptible *Staphylococcus aureus*) compared with the negative control group (samples exposed to neither CUR nor light) [41]. The authors also evaluated different CUR concentrations (5, 10 μM) and observed that all concentrations promoted viability reduction, however, the best protocol was the one that used CUR at 20 μM, suggesting that the efficacy against MRSA is directly proportional to the CUR concentration [41].

3.7. Citotoxixity

An ideal photosensitizer should have low toxicity to the host cells and high toxicity to the target cells when associated with illumination [76,77]. Thus, several studies have investigated the cytotoxic effects of CUR-mediated PDI on host cells [7,25,41,44,51] in order to establish a protocol that can be used in the clinical routine with safety.

Various types of cells (immortalized macrophage cell line [6], L929 fibroblasts [41], odontoblast-like cells [44], undifferentiated pulp cells [44] and human embryonic stem cells [44]) were used to perform the tests. In general, almost all authors concluded that the PDI protocols showed some effect in the cells, suggesting destruction in the plasma membrane (20 and 40 μM in 10% DMSO; PIT: 20 min; 5.28 and 37.5 J/cm^2) [7,41], reduction of cell metabolism [41] and less mitochondrial activity (ethanoic CUR at 10 μM in distilled water associated to LED for 5 min) [44].

In vivo investigations were conducted only in mice [25,51]. Slight inflammation on the supraspinous layer of the mice's oral mucous membranes (CUR at 1 M in Glycerin associated with 400 mW/cm^2 for 5 min) [51] was reported. On the other hand, Dovigo et al. [25] investigated the PDI (80 μM in 10% DMSO; PIT = 20 min; 37.5 J/cm^2) in a murine model of oral candidiasis and no changes in the superficial layer of the tongue were observed.

It is possible that the difference observed in the results occurred due to the distinct PDI protocols studied, as well as the different types of cells evaluated and the CUR formulations. According to Bruzell et al. [76], the phototoxic effects induced by CUR can be highly dependent on the type of preparation used. It is important to highlight that depending on the solvent used to dilute the CUR, the drug will be (or not) able to rapidly penetrate through the biological membranes and cellular barriers by the production of the structural defects in the membrane [76,77], resulting in the cytotoxic effects described above.

3.8. Cancer studies

Anti-cancer PDT is already established in the scientific community and several studies have indicate its efficacy [5,35,36,78–84]. However, most of them use another kind of photosensitizing drug [9,79,81,82]. According to our eligibility criteria, only 3 articles were able to be included in our revision, of which 2 are original articles and 1 is a review [35,36,78].

In general CUR seems to be an effective photosensitizing drug used in PDT due its capacity to induce ROS formation, as well as its properties against various kinds of cancer cells [36,78]. Nevertheless, Chan [35] observed that CUR concentrations higher than 100 μM completely blocked the photodynamic effect against human epidermal carcinoma (A431 cells). This result may have possibly occurred because higher CUR concentrations hinder the light penetration on samples and this fact is able to inhibit the ROS, considered the initiator of events that culminate in apoptosis [8–10,35]. In addition, the fact that the authors had used a conventional lamp without a wavelength specification to perform the illumination and kept the light in a distance of 30 cm from the samples may have influenced the negative result.

Park et al. [36] had used an uncommon light source for PDT (CUR at 40 μM; PIT: 20 min; 100 mJ/cm^2 of UVB light at 290–320 nm) and observed that this protocol was able to promote apoptosis in the keratinocyte cell (HaCaT), reducing surviving cancer cells by DNA fragmentation and proteinase activation more than CUR and UVB irradiation per se. The authors performed survival colony staining in HaCaT cells 3 days after PDT and result showed that the number of survival colonies was lower in PDT-treated HaCaT cells, compared to UVB or CUR alone. The authors also verified that the releasing of cytochrome c and reduction of procaspase-9 were more prominent when PDT was performed using sub-apoptotic concentration (10 μM) of CUR, suggesting that apoptosis is also mediated by mitochondrial signal pathways. It is an interesting result, since the absorption range of CUR fluctuates approximately between 300 and 500 nm, and the peak of maximum light absorption reaching close to 430 nm [7]. With this knowledge, it was expected that a higher efficacy of PDT happened in protocols using sources that emits close to the peak, once the CUR concentration used was low. On the other hand, the use of low CUR concentration might penetrate more easily into the cells, promoting higher sensitization.

3.9. The problem of the solubility and the stability

CUR has showed higher in vitro efficacy against oral microorganisms [6–15,24,25,40–50]. However, apart from its efficacy, CUR is a hydrophobic polyphenol with no aqueous solubility and poor bioavailability. Thereby, constant investigations have suggested some possible ways to increase its biopharmaceutical properties [24,45–49,85–89].

As previously reported by Bruzell et al. [76], the phototoxic effects induced by CUR can be highly dependent on the type of preparation used. Depending on the solvent used, CUR, which has an absorbance

spectra around 450 nm (300–500 nm), can present distinct optical and chemical comportment, resulting in higher or lower photodynamic effectiveness [25]. Another point that has to be reported is the fact that CUR has low stability after being manipulated, having a high rate of photodegradation, requiring its use almost immediately after handling [7,45–47,49].

In the present review, several types of solvents were used to dilute the CUR, and the most common (in 38.5% of studies) was a polar aprotic solvent (dimethyl sulfoxide, DMSO) [6–8,12,15,24,25,41,42,48]. Approximately 15.4% of studies did not specify [13,35,36,50,78] the solvent used and 46.1% of the studies evaluated different vehicles to dilute the CUR [9–11,14,43–47,49,51]. In general, most of the studies obtained good results after using the PDT technique [6–15,24,25,36,41–51], indicating that the chosen vehicles for the tests can be used to dilute the CUR. However, among the studies that assessed the PDT technique using CUR diluted in DMSO, the PDI protocol with the lowest photodynamic effect was presented by Leite et al. [24] (CUR at 30 mg/L in 0.1% DMSO; 200 J/cm^2), which promoted a reduction of one log of the saliva's microorganisms. Probably, the results found by Leite et al. [24] were due to the oral cavity environment and mainly because each microorganism in saliva may respond differently to treatment. In addition, the low concentration of DMSO might have restricted CUR penetration inside the cells.

Currently, although DMSO is the best CUR solvent, it is not an optimal vehicle for in vivo applications [76,77] due its cytotoxicity, which can cause damage in the structure of cell membranes and the cell wall [25,76,77]. Additionally, DMSO can promote tissue damage and undesired systemic effects [25,76,77]. Thus, several studies have evaluated different vehicles as efficient as DMSO for the CUR to exert photokilling against bacterial strains and tumor cells in order to permit its safe clinical use [9–11,14,43–47,49]. Among the studies that employed different excipients for the CUR, only one obtained an outcome with low efficacy (lyophilizate CUR) [47], although reduction of 2 log in microorganism viability was achieved.

In addition, nanotechnology strategies for CUR delivery have been studied over the past years. A diverse array of novel preparations have been developed, in which CUR is encapsulated in nanoliposomes, nanoparticles, microspheres, microemulsions, solid dispersions, dendrimers and dimers, among others [86–89]. The emphasis on nanorange formulations of CUR (known as nanocurcumin) has been mostly limited to in vitro models of cancer, but some investigations have shown that the formulations have also potential for the treatment of other chronic and life- threatening diseases [86–91]. In general, these approaches shed light on the development of new CUR formulations, but it seems that a more advanced level of investigations are needed to ensure pharmaceutical efficacy without toxicity problems.

4. Discussion and future directions

Over the years, PDT has emerged as a promising therapeutic protocol for the treatment of malignant and non-malignant diseases. Currently, several investigations regarding the use of PDI for reducing microorganisms have been performed due to the increase of the resistant microorganisms to the antifungal and antibacterial agents. In vitro and in vivo experiments showed that low CUR concentration is sufficient for the photodynamic efficacy against tumor cells and microorganisms if the technique is associated to blue LED light irradiation.

Different antimicrobial protocols using CUR have been investigated which promoted viability reduction of different oral pathogens. In general, the reported log-reductions ranged from 7 to "zero" log. According to Jori et al. [18], the efficacy of a PDI protocol can be measured by the minimal photosensitizer concentration which induces a 4 log drop in survival for a given set of irradiation parameters. Thus, most of CUR-mediated PDI protocols achieved such efficacy.

In addition, it seems that the PIT has an important function in order to obtain better results for the PDT and PDI, and the treatment with light alone and CUR alone did not show important cytotoxic effect. Besides, DMSO is the most studied excipient and shows high efficacy in microorganism's reduction, however it is necessary to highlight that this organic solvent has cytotoxic effects, especially in oral cavity.

Although in general the efficacy of CUR-mediated PDT/PDI has been verified, there are several different results among the studies and these differences may be explained due to the diversity of the CUR concentrations used, the variety of CUR solvents, type of CUR used, distinct PITs utilized, the diversity of species of microorganisms evaluated, as well as the different strains in the same species, the growth mode of the microorganisms (planktonic or biofilm), the different types of light sources, and the fluencies used. Hence, it can be difficult to compare the results of effectiveness when the parameters are completely distinct.

There is a reasonable number of in vitro studies showing the potential of the CUR-mediated PDT/PDI and their findings represent important progress to this field. However, only in vivo studies can definitively establish an effective protocol. Thus, in situ and in vivo investigations are necessary to establish a PDI protocol that can be clinically used with safety.

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