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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**