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Antimicrobial and anticancer applications and related mechanisms of curcumin-mediated photodynamic treatments

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ABSTRACT

Background: Curcumin has gained increasing attention in recent years due to its biological properties and photosensitivity. Curcumin-mediated photodynamic therapy has been used in antibacterial and anticancer applications. Considering the importance and rapid advances in curcumin-mediated photodynamic treatments and its related beneficial functions, a comprehensive and up-to-date review is timely to summarize the state-of-art in this area and to suggest directions for future progress.

Scope and approach: In this review, photodynamic therapies (PDT) with curcumin as photosensitizers are discussed, with particular emphasis on their application in anticancer and antibacterial therapies. Through photodynamic activation, enhanced therapeutic effect of curcumin is readily exhibited towards cancer and bacterial treatments. In addition, modification of curcumin with metal complexes and encapsulation of curcumin in nano delivery systems to enhance the PDT effect are discussed. Special emphasis is given to the mechanisms of curcumin-related PDT and to suggest future directions for progress.

Key findings and conclusions: The key finding of this review is that curcumin in combination with PDT can enhance the therapeutic effects of native curcumin against microbiota and cancer cell lines. However, there is still a lack of curcumin-PDT *in vivo* studies, and targeted delivery of curcumin has not yet been studied sufficiently, despite clear evidence for its potential. For future studies, more *in vivo* studies are needed, and the nano-delivery systems for curcumin can be modified with aptamers to realize targeted delivery and to enhance the PDT effect.

1. Introduction

Antibiotic resistance and malignancy are two leading global health challenges currently threatening public health. Conventional anticancer approaches, such as surgery, chemotherapy, and radiotherapy have been developed, but serious side effects often occur with conventional therapies. Antibiotic resistance has become a critical threat to effective antibacterial interventions. In order to minimize the threats, there is an increasing demand for more efficient approaches for anticancer and antibacterial agents.

Photodynamic therapy (PDT) is considered as a minimally invasive therapy, which may have significant advantages over conventional approaches, such as fewer side effects, high spatiotemporal precision, and fast healing of healthy tissues (Pinto da Silva et al., 2019). The therapeutic effect of PDT is based on the principle that photosensitizer (PS) accumulated in target cells or tissues can be activated by absorbing appropriate light energy to produce reactive oxygen species (ROS), thereby destroying biomolecules such as proteins, lipids, and nucleic acids. Nowadays, PDT has been applied to a variety of local pre-malignant conditions, solid tumors, and overcoming antibiotic resistance. In this context, numerous investigations were initiated to study PDT, and suggested this therapy in cases of microbial resistance, or in combination with conventional therapies to enhance therapeutic effects (Santezi, Reina, & Dovigo, 2018).

Previous studies reported that several synthetic dyes and natural pigments can be used as PS for PDT (Abrahamse & Hamblin, 2016; Siewert & Stuppner, 2019). Despite higher stability of synthetic dyes, natural pigments are more attractive, mainly because they may be less prone to incidental effects and adverse drug interactions (Santezi et al., 2018). Curcumin is a bright yellow compound (Fig. 1) that was first isolated from the rhizomes of turmeric by Vogel and Pelletier in 1842 (Aggarwal et al., 2006). Curcumin has shown diverse bioactivities, such

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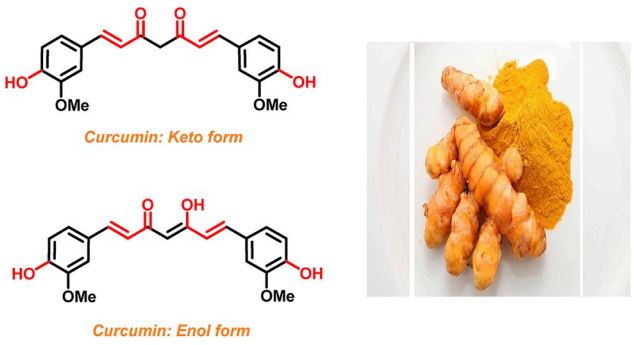

Fig. 1. The structure and picture of curcumin.

as anticancer (Beyer et al., 2017), antioxidant, anti-inflammatory, antimicrobial (Hussain et al., 2017; Schraufstätter & Bernt, 1949), neuroprotective, and antibiofilm formation effects (da Silva et al., 2018). Curcumin has also shown great potential as a PS because it is light sensitive and can absorb blue light. Growing evidence shows promising applications of curcumin as a PS against cancer and bacterial infection (Tables 1–4). Several studies have focused on modifying curcumin with metal-bound complexes or hybridizing curcumin with nanoparticles to enhance its PDT effects, with encouraging outcomes. Given the importance and rapid development of curcumin as a PS and its associated beneficial effects on PDT, a comprehensive and up-to-date review is timely to better understand current research advances and to encourage additional research.

This review points out challenges associated with antibacterial and anticancer activities of curcumin, and summarizes recent research progress on the photo-triggered antimicrobial and anticancer activities of curcumin and curcumin nanoparticles (curcumin-NPs). Special attention is given to the photo-cytotoxicity mechanisms of curcumin and its nanoformulations. This review mainly focusses on the latest five-year time period of the English articles from the Web of Science Core Collection, and aims to provide a comprehensive and updated understanding of the antimicrobial and anticancer effects of curcumin-PDT/curcumin-NPs-PDT, which may stimulate its further development as a promising natural photosensitizer.

2. Challenges associated with antimicrobial and anticancer activities of curcumin

The application of curcumin is hampered due to its poor bioavailability, such as rapid elimination, poor gastrointestinal absorption, and poor aqueous solubility (Imran et al., 2018). In the gastrointestinal tract, curcumin metabolism involves several reactions, such as glucuronidation, sulfation, and reduction reactions, resulting in poor systemic absorption (Ireson et al., 2002). In addition, most of the ingested curcumin does not enter the bloodstream, because about 40–80% of the total ingested curcumin is undigested in the gastrointestinal tract and curcumin metabolites have very poor cell permeability and short half-life (Imran et al., 2018). When rats were administered 40 mg/kg curcumin intravenously, it was untraceable in plasma within 1 h, and when rats were administered 500 mg/kg curcumin orally, its peak plasma concentration was only 1.8 ng/mL (Ireson et al., 2002).

To circumvent the drawbacks of curcumin, much effort has been made to improve its systemic bioavailability, such as by developing curcumin nanoparticles, modifying curcumin with metal-bound complexes, or combining with other therapeutic agents. Furthermore, curcumin and curcumin-based nanoparticles have been combined with light, some of which exhibit promising antimicrobial and anticancer activities, as discussed in detail below.

3. Antimicrobial and anticancer activities of curcumin-PDT

3.1. Antimicrobial activity of curcumin-PDT

The antimicrobial activity of curcumin-PDT on various microorganisms has been widely investigated (Table 1), especially the potential against *Staphylococcus aureus* (*S. aureus*). When *S. aureus* cells were treated with curcumin and blue light (470 nm), many cells with pits were observed, indicating that curcumin-PDT destroys the structure of bacterial cell membranes leading to cell death (Jiang, Leung, Hua, Rao, & Xu, 2014). In addition, curcumin-PDT inhibited the growth of *S. aureus* (Tortik, Spaeth, & Plaetzer, 2014) and *Staphylococci* (Almeida et al., 2017) on foods.

Streptococcus mutans (*S. mutans*) is the major pathogen causing dental caries, and the antibiotic resistance of *S. mutans* has elevated in recent years due to the overuse of antibiotics. To eradicate antibiotic-resistant *S. mutans*, curcumin-PDT was utilized. It was reported that curcumin-PDT can reduce the number of viable cells of *S. mutans,* but has little effect on its biofilm (Panhóca et al., 2016; Paschoal et al., 2013; Paschoal, Lin, Santos-Pinto, & Duarte, 2015; Paschoal, Santos-Pinto, Lin, & Duarte, 2014). Similar conclusions were reported by Manoil et al. (2014) and Lee, Kang, Jeong, Chung, and Kim (2017).

Curcumin-PDT was also been used to eradicate *Escherichia coli* (*E. coli*) and *Listeria innocua* (*L. innocua*). de Oliveira, Tosati, Tikekar, Monteiro, and Nitin (2018) reported that curcumin in combination with UV-A light could inactivate bacteria in food systems. It was noteworthy that curcumin exhibited higher antibacterial efficiency towards *L. innocua* biofilms than porphyrin (Bonifacio et al., 2018). Since curcumin has poor water solubility, Wikene, Bruzell, and Tonnesen (2015) applied natural deep eutectic solvents to dissolve curcumin, whereby curcumin photoinactivated *E. coli* at a lower concentration than observed in any previous investigation. In addition, Spaeth, Graeler, Maisch, and Plaetzer (2017) pointed out that curcumin modified with cationic charge exhibited 100 times higher antibacterial effect than natural curcumin. Other groups also found that modification of curcumin with cationic charges could strongly enhance antibacterial effect against *S. aureus* and *E. coli* (Glueck, Schamberger, Eckl, & Plaetzer, 2017; Tortik, Steinbacher, Maisch, Spaeth, & Plaetzer, 2016), which can be inhibited by curcumin up to 99% and 95%, respectively (Condat et al., 2015).

Antifungal studies of curcumin and curcumin-PDT were conducted against *Candida albicans* (*C. albicans*) in the presence and absence of light (Al-Asmari, Mereddy, & Sultanbawa, 2017; Pellissari et al., 2016). All these studies demonstrated that light irradiation in combination with curcumin could reduce fungal growth. In addition, combined photodynamic and chemical treatment could inhibit *C. albicans* significantly ($p < 0.05$) (Hsieh et al., 2018). But Soria-Lozano et al. (2015) pointed out that PDT with curcumin was less effective against fungal infection compared to other photosensitizers such as Methylene Blue and Rose Bengal, which should be taken into consideration in future studies.

Aggregatibacter actinomycetemcomitans (*A. actinomycetemcomitans*) is an opportunistic periodontopathogen with various virulence factors that can resist clearance attempts through its protective extracellular matrix (Pourhajibagher et al., 2018). Curcumin-PDT was applied to inhibit the growth of *A. actinomycetemcomitans* and reduce the expression level of *rcpA* gene, a virulence factor associated with biofilm formation (Pourhajibagher et al., 2018). This study pointed out that curcumin-PDT could significantly reduce the biofilm formation and viability of *A. actinomycetemcomitans*. Similar conclusions were also obtained by Najafi et al. (2016) and Saitawee, Teerakapong, Morales, Jitprasertwong, and Hormdee (2018).

Curcumin-PDT has also been applied effectively to eradicate other microbiota, such as *Lactobacilli spp*, *Vibrio parahaemolyticus* (*V. parahaemolyticus*), *Trichophyton rubrum* (*T. rubrum*), *Candida dubliniensis* (*C. dubliniensis*), *Propionibacterium acnes* (*P. acnes*), and *Staphylococcus*

Table 1
Antimicrobial activities of photo-activated curcumin formulations.

Curcumin formulations	Tested microorganisms	Treatment conditions	Without PDT	PDT	Units	Outcomes	Ref.
Curcumin	*S. mutans*	2000, 4000, and 8000 μM curcumin, blue LED light (450 nm, 240.1 mW/cm^2, 24, 48 and 72 J/cm^2)	7.05–7.20	2.16–5.98	CFU $\log_{10}$ mL^{-1}	Generation of ROS	Paschoal et al. (2013)
Curcumin and toluidine blue	*S. mutans*	0.75 μM curcumin, blue light (550 nm, 3410 mW/cm^2, 42 J/cm^2)	5.36	0	CFU $\log_{10}$ mL^{-1}	Generation of ROS	Paschoal et al. (2014)
Curcumin	*S. mutans*	0.2 μM curcumin, blue light (360–550 nm, 450 mW/cm^2, 2 min)	25%	6%	Live cells	Damage membranes	Manoil et al. (2014)
Curcumin	*S. mutans*	2.5, 1.25, and 0.75 mM curcumin, blue LED light (420 nm, 95.5 mW/cm^2, 24, 48 and 72 J/cm^2)	5.02–5.17	0	CFU $\log_{10}$ mL^{-1}	ROS production and curcumin interaction with the target cell organelles	Paschoal et al. (2015)
Curcumin	*S. mutans*	1.5 mg/ml curcumin, blue LED light (450 nm, 0.764 mW/cm^2, 45 J cm^{-2})	5.33	4.96	CFU $\log_{10}$ mL^{-1}	Curcumin attached to the bacterial walls and penetrated into the bacteria	Panhóca et al. (2016)
Curcumin	*S. mutans*	10 ng/ml curcumin, visible light (405 nm, 84.5 mW/cm^2, 25.3 J/cm^2)	6.29	0	CFU $\log_{10}$ mL^{-1}	Cell penetration and photoreaction	Lee et al. (2017)
		10^2 ng/ml curcumin, visible light (405 nm, 84.5 mW/cm^2, 25.3 J/cm^2)	6.41	0			
		10^3 ng/ml curcumin, visible light (405 nm, 84.5 mW/cm^2, 25.3 J/cm^2)	6.46	0			
		10^4 ng/ml curcumin, visible light (405 nm, 84.5 mW/cm^2, 25.3 J/cm^2)	6.37	5.67			
Curcumin bound to polyvinylpyrrolidone (PVP–C) and NovaSol®-curcumin	*S. aureus*	50 and 100 μM curcumin, visible light (435 nm, 9.4 mW/cm^2, 33.8 J/cm^2)	1.1×10^7–2.8×10^7	6.5×10^4–1.5×10^5	CFU/mL	ROS generation	Tortik et al. (2014)
Curcumin	*S. aureus*	2.5 μM curcumin, blue light (470 nm, 60 mW/cm^2, 3 J/cm^2)	≈8.3	≈6.0	CFU $\log_{10}$ mL^{-1}	Damage bacteirial membrane permeability and increase ROS generation	Jiang et al. (2014)
Curcumin	*S. aureus* biofilms	1.5 g/L curcumin, light (450 nm, 67 mW/cm^2, 20.1 J/cm^2)	≈4.5	3.666	CFU $\log_{10}$ mL^{-1}	Reduce *S. aureus* biofilms	(Dantas Araujo et al., 2018)
Curcumin	*S. aureus* biofilms	1.25 mg/mL, light (450 nm, 35 mW/cm^2, 50 J/cm^2)	–	136	CFU/mL	Reduce biofilm formation	Zangirolami et al. (2018)
Curcumin	*S. aureus*	1.5% curcumin, LED light (450 nm, 75 mW/cm^2, 54 J/cm^2)	1.5×10^4	1.5×10^2	CFU/mL	PDT controls *Staphylococci intradermal* infection and is effective against methicillin-resistant *S. aureus* infection in a murine model of intradermal infection	Almeida et al. (2017)
Curcumin	*E. coli*	2.60 μM curcumin, light (310–800 nm, 765 mW/cm^2, 27 J/cm^2, 30 min)	–	> 6	Log-reduction of CFU/mL of viable *E. coli*	Curcumin dissolving in natural deep eutectic solvents (NADES) can photoinactivate *E. coli* at lower concentrations	Wikene, Bruzell, et al. (2015)
Cationic curcumin derivative SACURCUMIN-3	*E. coli*	50 cationic curcumin derivative SACURCUMIN-3, light (435 nm, 9.4 mW/cm^2, 33.8 J/cm^2)	1	5.6	CFU_{Co} $_{-/-}$/CFUsample	This method improves the microbiological safety of plant food with a flat or spherical geometry	Glueck et al. (2017)

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Table 1 (*continued*)

Curcumin formulations	Tested microorganisms	Treatment conditions	Without PDT	PDT	Units	Outcomes	Ref.
Curcumin	*E. coli* O157: H7 and *L. innocua*	5 curcumin, UV-A light (320–400 nm, 32 mW/cm^2, 5 min)	6	1	CFU $\log_{10}$ mL^{-1}	Inactivate bacteria in food systems	de Oliveira et al. (2018)
Curcumin-rich extract of *Curcuma longa* or commercial Curcumin	*L. innocua* biofilms	3.7 mg/L curcumin, blue light (400–500 nm, 150 mW/cm^2, 30min)	≈4	≈2	CFU/mL	Inactivate *Listeria* biofilms	Bonifacio et al. (2018)
Curcumin	*S. mutans* and *L. acidophilus* and their biofilms	0.75, 1.5, 3.0, 4.0, and 5.0 g/L curcumin, blue light (450 nm, 19 mW/cm^2, 5.7 J/cm^2)	≈85%	≈0	Bacterial survival	Reduce cell viability in the biofilm phase while having less effect on the microorganisms within dentine carious lesions	Araujo, Fontana, Bagnato, and Gerbi (2014)
Curcumin	*S. mutans* and *L. acidophilus*	5.0 g/L curcumin, blue light (450 nm, 19 and 47.5 mW/cm^2, 5.7 J/cm^2)	≈100%	≈30%	Bacterial survival	Phototoxic towards microorganisms at appreciable concentrations	Araujo et al. (2017)
Cationic derivative of curcumin (SACURCUMIN-3) to curcumin bound to polyvinylpyrrolidone (PVP-CURCUMIN)	*S. aureus* and *E. coli*	100 μM SACURCUMIN-3 and PVP-CURCUMIN, blue light (435 nm, 9.4 mW/cm^2, 33.8 J/cm^2)	1.1–3.4 × 10^7	2.3 × 10^4–2.0 × 10^7	CFU/mL	Cationic curcumin derivative SACURCUMIN-3 is effective against Gram (+) and Gram (−) pathogens, but the formulation of PVP-CURCUMIN is only effective against Gram (+) pathogens	Tortik et al. (2016)
Curcuminoids bearing cationic substituents	*E. coli* and *S. aureus*	0–500 μM PS, blue light (435 nm, 9.4 mW/cm^2, 33.8 J/cm^2)	≈ 10^7	≈ 10^2	CFU/mL	Exhibit at least 100-fold more effective antibacterial effect than natural curcumin	Spaeth et al. (2017)
Curcumin	*E. faecalis*	20 μM PS, blue light (450 nm, 100 mW/cm^2, 5 min)	5.98 × 10^8	3.64–5.22 × 10^8	CFU/mL	Curcumin as a photosensitizer was not effective in eliminating *E. faecalis*	da Frota et al. (2015)
Methylene blue, chlorin-e6, and curcumin	*E. faecalis* and *P. acnes*	17–136 μM curcumin, blue light (450 nm, 151 mW/cm^2, 3.12–25 J/cm^2)	-	33.2–100%	Reduction	Reduce bacteria	de Annunzio et al. (2018)
Peptide aurein 1.2, methylene blue, chlorin-e6, and curcumin	*E. faecalis*	17, 34, 68 μM curcumin, blue light (450 nm, 155 mW/cm^2, 12.5 J/cm^2)	–	5.2%	Reduction	Aurein 1.2 is capable of enhancing the PDT activity whenever mediated by methylene blue or chlorin-e6, but not by curcumin, revealing a PS-dependent mechanism	de Freitas et al. (2018)
Curcumin and sodium hypochlorite	*E. faecalis* bioflm	2.5 mg/ml curcumin, blue light (380–515 nm, 1200 mW/cm^2, 4 min)	4.2–4.8 × 10^4	0	CFU/mL	Light activation exhibited remarkably higher antibacterial efficacy than ultrasonic agitation, with light activated curcumin producing the maximum elimination of biofilm bacteria within the root canal lumen and dentinal tubules	Neelakantan et al. (2015)
Curcumin, triple antibiotic paste, double antibiotic paste, chlorhexidine, and calcium hydroxide	*E. faecalis* bioflm	2.5 mg/ml curcumin, blue light (380–515 nm, 1200 mW/cm^2, 4 min)	2.3–4.8 × 10^8	1.1–3.7 × 10^2	CFU/mL	Exhibit antibiofilm efficacy	Devaraj, Jagannathan, and Neelakantan (2016)
Curcumin	*C. albicans*	2.5 μM curcumin, blue light (455 nm, 89.2 mW/cm^2, 37.5 J/cm^2)	≈16	≈117	Tail length (μm) representing DNA damage	ROS formation and DNA damage	Carmello et al. (2015)
Curcumin	*C. albicans*, *C. glabrata*, and *S. mutans* bioflms	120 μM curcumin, blue light (440–460 nm, 22 mW/cm^2, 37.5 J/cm^2)	≈6.5	≈5.5	CFU $\log_{10}$ mL^{-1}	Inactivate multispecies biofilm	Quishida et al. (2016)
Curcumin	*C. albicans* and epithelial cells	40 μM curcumin, blue light (455 nm, 5.28 J/cm^2, 4 min)	6.51	5.39	CFU $\log_{10}$ mL^{-1}	Inhibit the growth of keratinocytes and *C. albicans* in all tests	Pellissari et al. (2016)
Curcumin	*C. albicans*	1–80 μM curcumin, blue light (450 nm, 9 J/cm^2, 30 min)	≈5	0	CFU $\log_{10}$ mL^{-1}	Inhibit bacterial growth	Hsieh et al. (2018)

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Table 1 (*continued*)

Curcumin formulations	Tested microorganisms	Treatment conditions	Without PDT	PDT	Units	Outcomes	Ref.
Curcumin	*S. sanguis*, *S. mutans,* and *C. albicans*	80–1280 μg/ml curcumin, blue light (430 nm, 90 μW/cm^2, 37 J/cm^2)	–	5 - 6 $\log_{10}$	Reduction	Kill these bacteria but curcumin is the least effective and methylene blue is the most efficient	Soria-Lozano et al. (2015)
Curcumin	*A. niger*, *A. flavus*, *P. griseofulvum*, *P. chrysogenum*, *F. oxysporum*, *C. albicans*, and *Z. bailii*	100–1000 μM curcumin, light (370–680 nm, 0–96 J/cm^2, 0–8 min)	≈1–15%	≈50–100%	Reduction	Against fungal spores/cells, and the effect was dependent on curcumin concentration, light dosage, and fungal species	Al-Asmari et al. (2017)
Curcumin	*A. flavus*	15 μM curcumin, light (420 nm, 0–84 J/cm^2)	≈3.2	≈0	Log mean CFU mL^{-1}	Decontaminate *A. flavus* spores in foods and feeds	Temba, Fletcher, Fox, Harvey, and Sultanbawa (2016)
Curcumin	*A. mcomitans*, *P. gingivalis,* and *P. intermedia*	blue light (470 nm, 620 mW/cm^2, 5 min)	≈6	≈21–41%	Reduction	Reduce bacteria	(Sreedhar et al., 2015)
Chlorhexidine digluconate and curcumin	*A. mcomitans*	5 mg/ml curcumin, light (420–480 nm, 400 mW/cm^2, 24–120 J/cm^2)	6.45–7.65	4.55–6.48	Log CFU mL^{-1}	PDT can enhance the antibacterial effect of curcumin	Najafi et al. (2016)
Curcumin	*A. mcomitans*	10–40 μmol/ml curcumin, light (450 nm, 1000–1400 mW/cm^2, 180–240 J/cm^2)	–	30.8%	Reduction	Reduce bacteria and the expression of the *rcpA* gene	Pourhajibagher et al. (2018)
Curcuma longa extract	*A. mcomitans*	0.39–1.56 μg/ml curcumin, light (420–480 nm, 280 mW/cm^2, 16.8 J/cm^2)	–	0	Log_{10} CFU mL^{-1}	Significantly inhibit the growth of bacteria	Saitawee et al. (2018)
Curcumin, eosin Y, and rose bengal	*Lactobacilli*	400 μM Curcumin, blue light (380–500 nm, 4 min)	≈95%	≈1–5%	Live bacteria	Significantly reduce bacterial viability	Bulit et al. (2014)
Curcumin	*V. parahaemolyticus*	5, 10, 20 μM curcumin, light (470 nm, 0.06 mW/cm^2, 3.6 J/cm^2)	≈4.2	0	Log CFU mL^{-1}	Significantly reduce bacterial viability	Wu et al. (2016)
Curcumin	*G. mellonella* and larvae of *G. mellonella*	100 μM curcumin, light (405 nm, 10, 20, 30 J/cm^2)	16.09%	100%	Inhibition rate	PDT is potent against bacterial infections	Merigo et al. (2017)
Curcumin	T. rubrum, T. interdigitale, T. terrestre, M. canis, M. gypseum, and E. floccosum	5.4 mg/L curcumin, visible light (367 nm, 900 mW/cm^2, 5 J/cm^2)	≈0.250	≈0.050	OD_{620}	Significantly suppress bacterial infections	Brasch, Freitag-Wolf, Beck-Jendroschek, and Huber (2017)
Curcumin	*T. rubrum*	2.5–20 mg/ml curcumin, light (420 nm, 20 J/cm^2, 8 min)	≈0.50	≈0.050	OD_{620}	Curcumin dissolving in DMSO plus irradiation had a marked dose-dependent inhibitory effect on fungal growth but micellar curcumin had no inhibitory effect	Brasch, Beck-Jendroschek, and Mahn (2018)
Curcumin	*C. dubliniensis* bioflm	20, 30, 40 μM curcumin, light (455 nm, 22 mW/cm^2, 5.28 J/cm^2)	4.40×10^5–3.10×10^6	0	CFU/mL	Reduce the metabolism of the biofilm organized cells of *C. dubliniensis*	Sanita et al. (2018)
Curcumin	*P. acnes*	1.56 μM curcumin, blue light (462 nm, 3.0 mW/cm^2, 0.09 J/cm^2)	0	≈100%	Inhibition rate	Decrease the viability of *P. acnes*	Yang, Chang, Chen, and Hu (2018)
Curcumin	Infected dentin caries microcosms	600 μM curcumin, blue light (455 nm, 0, 37.5, 75 J/cm^2)	≈7	≈5	CFU $\log_{10}$ mL^{-1}	Reduce infected dentin caries microcosms	Mendez et al. (2018)
Curcumin, EDTA	*B. cepacia*	125 μM curcumin with 0.4% (w/v) EDTA, blue LED light (425 nm, 16 mW/cm^2, 30 min)	≈95%	≈60%	Viability	Induce protein degradation and genomic DNA cleavage	Hu et al. (2018)

Table 2
Anticancer activities of photo-activated curcumin formulation.

Curcumin formulations	Tested cells	Treatment conditions	Outcomes	Potential mechanisms	Ref.
Curcumin	human oral squamous cell and carcinoma cell	0.01–1 μg/ml curcumin, UVA (1 J/cm^2, 5min)	Enhance anticancer effect of curcumin	Disrupt the membrane integrity and impair DNA synthesis	Beyer et al. (2017)
Curcumin	Human glioma cells	25 μM curcumin, blue light (460 nm, 70 mW/cm^2, 60 J/cm^2)	Decrease cell viability	–	Jamali, Hejazi, Ebrahimi, Moradi-Sardareh, & Paknejad (2018)
Curcumin	HuH6, HepT1, HepG2, HC-AFW1	1–100 μg/ml curcumin, blue light (480 nm, 300 W, 1, 3, 6 h)	Decrease cell viability	Generation of ROS	Ellerkamp et al. (2016)
Demethoxycurcumin (DMC)	A431 and HaCaT cells	40 μM DMC, UVB (460 nm, 50 J/cm^2)	Increase cell apoptosis	Activate p53 and caspase pathways, upregulate Bax and p-p65 expression and downregulate Bcl-2, Mcl-1, and nuclear factor-κB expression	Xin et al. (2017)
Chlorin e6-curcumin (Ce6-curcumin)	Pancreatic cancer cells and AsPC-1 cells	0–50 μM Ce6-curcumin, light (660 nm, 50 mW/cm^2, 2 J/cm^2)	Induce enhanced cell apoptosis	Upregulate the expression of BAX, Cytochrome-C, and cleave caspase 9, while downregulate the Bcl-2 expression an anti-apoptotic protein marker	Jalde et al. (2018)
Ferrocenyl-terpyridine oxovanadium (IV) complexes of curcuminoids	HeLa and Hep G2 cancer cells	0.1–100 μM PS, light (400–700 nm, 10 J/cm^2, 1 h)	Induce enhanced cell apoptosis	Light-induced cell death by the complexes via an apoptotic pathway.	Balaji et al. (2014)
Oxidovanadium (IV) complexes of curcumin and (acridinyl) dipyridophenazine	HeLa and HaCaT cells	30 μM PS, light (400–700 nm)	Induce cell apoptosis	Photocleavage of supercoiled pUC19 DNA in red light by generating˙OH radicals as the ROS	Banerjee et al. (2014)
Oxidovanadium (IV) complexes of curcumin	HaCaT and MCF-7 cancer cells	15 μM PS, light (400–700 nm, 10 J/cm^2, 2 h)	Induce cell apoptosis	Selective mitochondrial localization and generate ROS inducing DNA photocleavage	Prasad et al. (2014)
Curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC)	MCF-7, MDA-MB-231, and MDA-MB-453 cells	–	Inhibit cell proliferation and induce autophagic and apoptotic responses	Activate MAPK pathway and inhibit AMPK activation	Lin et al. (2015)
Oxidovanadium (IV) complex of Curcumin	HeLa, MCF-7 cancer cells, and normal 3T3 cells	5 μM PS, light (400–700 nm, 10 J/cm^2, 1 h)	Induce cell apoptosis	Generate ROS, cleave plasmid supercoiled DNA to its nicked circular form.	Banerjee et al. (2015)
Ternary cobalt (III) complexes of curcumin and mitocurcumin	MCF-7 and HeLa cancer cells	10 μM PS, light (400–700 nm, 10 J/cm^2)	Induce cell apoptosis	Generate ROS	Garai et al. (2016)
Oxidovanadium (IV)-boron-dipyrromethene conjugates of curcumin	HeLa and MCF-7 cancer cells	2–6 μM PS, light (400–700 nm, 10 J/cm^2, 1 h)	Induce cell apoptosis	Generate ROS	Bhattacharyya et al. (2017)
Mixed-ligand cobalt (III) complexes of curcumin	MCF-10 A normal cells and HeLa cells	1.6–7.4 μM PS, light (400–700 nm, 10 J/cm^2, 1 h)	Non-toxic to normal cells and induce cancer cell apoptosis	Generate ROS	Sarkar et al. (2015)
Cobalt (III) chaperone complexes of curcumin	DLD-1 and MCF-7 tumor cells	50 μM PS, light (470 nm, 45.3 J/cm^2, 0–1 h)	Enhanced cell apoptosis	Generate ROS	Renfrew et al. (2015)
Methylene blue-curcumin and methylene blue-salicylic acid	MDA-MB-231 human breast cancer cells	10–100 μM PS, light (660 nm, 30 mW/cm^2)	Enhanced cytotoxicity	Increase molecular stability and prevent the dimerization of methylene blue, thus increase cell killing potential	Khorsandi et al. (2018)
Dinuclear iron (III) complex of curcumin	HeLa and MCF-7 cancer cells	0.01–100 μM PS, light (400–700 nm, 10 J/cm^2, 1 h)	Induce cell apoptosis	Generate ROS	Sarkar et al. (2016)
BODIPY appended copper (IJII) complexes of curcumin	HeLa cells	0.01–100 μM PS, light (400–700 nm, 10 J/cm^2, 1 h)	Induce cell apoptosis	Formation of ROS	Bhattacharyya et al. (2015)

Table 3
Antimicrobial activities of photo-activated curcumin nanoparticles.

Types of curcumin nanoparticles	Cargo	Tested microorganisms	Treat conditions	Cell survival for curcumin	Cell survival for nano-curcumin	Units	Highlights	References
Curcumin-nanoparticles	Curcumin	*T. rubrum*	10 μg/mL curcumin, blue light (417 nm, 10 J/cm^2, 17 min)	≈1.2 × 10^3	≈1.2 × 10^3	CFU/mL	Induce greater NO• expression	Baltazar et al. (2015)
Copper impregnated mesoporous silica nanoparticles (Cu-MSN) with immobilizing silver nanoparticles (SNP)	Curcumin	*E. coli*	20, 40, 80 μg/mL curcumin, light (410, 425, 428 nm, 72 J/cm^2, 5 min)	≈6.5	0	Log CFU/mL	Produce higher amounts of ROS under light irradiation	Kuthati et al. (2017)
Polyethylene terephthalate (PET) film	Curcumin/ cyclodextrin	*E. coli*	white light	–	2.4	△Log CFU/mL	Prolong release and stabilize curcumin	Shlar et al. (2018)
Polymeric PLGA nanoparticles	Curcumin	*C. albicans*, *C. neoformans*, and *S. epidermidis*	10 μM curcumin, light (420 nm, 200 mW/cm^2, 36 J/cm^2)	≈140	10	cells/mL	Prevent the degradation of curcumin	Pietra et al. (2017)
Polymeric nanoparticles	Curcumin	*S. mutans*, *C. albicans*, and methicillin-resistant *S. aureus*	light (455 nm, 33.58 mW/cm^2, 20 min)	≈7	≈0.5	$\log_{10}$(CFU/mL)	Improve water solubility of curcumin and reduce the cytotoxicity of 10% DMSO used for free curcumin	Gutierrez et al. (2017)
Edible hydrogel coatings	Curcumin	*L. innocua*	UV-A light (320–400 nm, 18 W, 8 cm, 32 W/m^2)	0	≈ −3	Log (CFU/mL)	Photo-irradiate low levels of curcumin releases from the coatings to solution	Tosati et al. (2018)
Microemulsions	Curcumin	*P. aeruginosa*	Blue light (455 nm, 12 cm, 16 mW/cm^2, 15 min, 14.4 J/cm^2)	≈30%	≈100%	Reduction	Photodynamic treatment damages bacterial morphology	Liu et al. (2016)

epidermidis (*S. epidermidis*) (Table 1). Importantly, Hu et al. (2018) reported that curcumin-PDT in combination with EDTA could reduce *Burkholderia cepacia* (*B. cepacia*) viability and induce large-scale protein degradation and genomic DNA cleavage. However, curcumin-PDT was not effective in eliminating *Enterococcus faecalis* (*E. faecalis*) (da Frota et al., 2015). This conclusion was also obtained by other three groups (de Annunzio et al., 2018; de Freitas et al., 2018; Neelakantan et al., 2015).

Curcumin-PDT can effectively eradicate bacterial and fungal biofilms. Curcumin-PDT could significantly ($p < 0.05$) inhibit the biofilm formation of *S. aureus,* increase the sensitivity of *S. aureus* to curcumin-PDT, reducing bacterial activity (Araujo et al., 2018; Zangirolami, Inada, Bagnato, & Blanco, 2018). Zangirolami et al. (2018) applied curcumin-PDT to destroy the biofilm of *S. aureus* achieving 70% biofilm reduction in conditions of 1.25 mg/mL curcumin, 2 h of PS incubation, and 50 J/cm^2. Also, Thomsen, Graf, Farewell, & Ericson. (2018) found that compared to free curcumin, curcumin-hydroxypropyl-gamma-cyclodextrin (HPγCD) complex combined with confined 2-photon excitation can destroy *S. epidermidis* biofilms. Moreover, HPγCD complex has shown high bioavailability in the biofilm and displayed subcellular localization within the bacteria. Panhóca et al. (2016) reported that curcumin-PDT can enhance the killing of *Streptocoocus mutans* biofilms *in situ*. Sanita et al. (2018) treated four *C. dubliniensis* biofilms with three different concentrations of curcumin (20.0, 30.0, and 40.0 μM) in combination with LED light (455 nm, 22 mW/cm^2, 5.28 J/cm^2), and found that PDT significantly ($p < 0.001$) reduced the biofilm by reducing the metabolic activity of yeast cells. Moreover, uptake of curcumin by yeast cells and penetration of curcumin within the biofilm is also enhanced. Curcumin-PDT has also been applied to inactivate multispecies biofilm. For instance, curcumin-PDT treatment could reduce the viability of denture stomatitis-associated biofilm-forming microbes such as *C. albicans*, *Candida glabrata (C. glabrata)*, and *S. mutans* (Quishida et al., 2016).

3.2. Anticancer activity of curcumin-PDT

The anticancer activity of curcumin-PDT has been investigated in various types of cancer cell lines, such as HeLa, HaCaT, HepG2, MCF-7, and MDA-MB-231 (Table 2). It is clear that different cancer cells respond differently to curcumin-PDT. PDT strongly enhanced the anticancer effect of curcumin in pediatric solid liver tumors (Ellerkamp et al., 2016), human glioma cells (Jamali, Hejazi, Ebrahimi, Moradi-Sardareh, & Paknejad, 2018), and oral mucosa cancer (Beyer et al., 2017), but did not inhibit the growth of L-929 fibroblasts (Gomes-Filho et al., 2016). This indicates that curcumin-PDT exhibits selective cytotoxicity towards cancer cells without damaging normal cells. In addition, demethoxycurcumin has been applied as a photosensitizer to attack A431 and HaCaT cells. The cancer cells treated with demethoxycurcumin-PDT exhibited increased apoptosis through the activation of p53 and caspase pathways, as well as through upregulation of Bax and p-P65 expression, and downregulation of Bcl-2, Mcl-1, and nuclear factor-kB expression (Xin et al., 2017).

Attempts have been made to combine popular PS with curcumin for synergistic anticancer effects in PDT (Pourhajibagher et al., 2016). Jalde et al. (2018) reported that combining curcumin with chlorin e6 as a photosensitizer showed higher generation of ROS and exhibited excellent PDT efficacy towards pancreatic cancer cells and AsPC-1 cells. Khorsandi, Chamani, Hosseinzadeh, and Hosseinzadeh (2018) applied curcumin-methylene blue as a photosensitizer in PDT to treat MDA-MB-231 human breast cancer cells and found that curcumin-methylene blue ion pair showed higher photodynamic efficacy than salicylate-methylene blue complex.

In order to improve the bioavailability of curcumin, Banerjee et al. (2012) modified curcumin structure with metal complexes, which can enhance the stability of curcumin in biological media, enhance photocytotoxicity, and can selectively deliver curcumin to cancer cells.

Table 4
Anticancer activities of photo-activated curcumin nanoparticles.

Types of curcumin nanoparticles	Cargo	Tested cancer cells/ animal model	Treatment conditions	Cell survival for curcumin	Cell survival for nano-curcumin	Potential mechanisms	Ref.
Nanomicelles	Curcumin	Solitary fibrous tumor cells	500 nM curcumin, blue laser light (445 nm, 150 mW/cm^2, 9 J/cm^2)	> 70%	≈0	Nanocarrier systems efficiently deliver curcumin to target cells, achieve substantial cytotoxic activity, affect EMT markers expression, and decrease cancer cell invasiveness	Dagrada et al. (2018)
PLGA nanoparticles	Curcumin	Glioblastoma tumor DKMG/EGFRvIII cells	10 μM curcumin, blue light (460 nm, 60 J/cm^2)	> 80%	≈40%	Realize target deliver drug to special cells	Jamali et al. (2018b)
Drug-loaded BSA nanoparticles	Curcumin	Glioblastoma stem cells	6 μM curcumin, blue light (450 nm, 1000 J/cm^2, 2.5 min)	≈80%	≈35%	Sustained release of the drug and prolongs the period of drug exposure	Dev et al. (2016)
Polydopamine nanoparticle	Chlorine6 and Curcumin	A549 cells and female Balb/c mice	0–1.2 μM curcumin, blue light (660 nm, 5 mW/cm^2, 40 min)	≈100%	≈20%	Increase intracellular uptake of the drug and Ce6 can trigger ROS generation, while curcumin as an excellent radiosensitizer	Yu et al. (2017)
Solid lipid nanoparticles (SLNs)	Curcumin	A549 cells	15 μM curcumin, blue light (430 nm, 50 mW/cm^2, 20 min)	≈50%	≈20%	Stock more cell cycle at G2/M phase, produce more ROS, increase the expression of caspase-3, caspase-9 proteins, and promoted the ratio of Bax/Bcl-2.	Jiang et al. (2017)
A self-monitored and self-delivered photosensitizerdoped FRET nanoparticle drug delivery system	Tetro (4-pyridyl) porphyrin and Curcumin	A549 cells and A549 tumor-bearing nude mice	250 μg/mL curcumin, blue light (400–700 nm, 150 W)	–	≈20%	Realize self-monitoring and self-delivery of drugs and enhance water solubility	Zhang et al. (2015)
Tetraether liposomes	Curcumin	SK-OV-3 cell line	0–100 μM curcumin, blue light (457 nm, 3.2 J/cm^2)	≈80–95%	≈20–35%	Increase ROS generation	Duse, Pinnapireddy, Strehlow, Jedelska, and Bakowsky (2018)
Doxorubicin-anchored curcumin nanoparticles	Curcumin and doxorubicin	HepG2 (human hepatoma cells)	0–120 × 10^{-6} M curcumin, 5 × 10^{-6} M/ml Doxorubicin, blue light (420 nm, 30 min)	≈30–100%	≈18–60%	ROS-mediated p53-dependent apoptotic pathway	Rajiu et al. (2015)
Chitosan/tripolyphosphate nanoparticles	Curcumin	Gastric cancer cells and non-cancer gastric cells	5 μM curcumin, blue light (460 nm, 5 mW/cm^2, 9 J/cm^2)	≈82%	≈30%	Generation of $^1O_2$	Tsai, Yu, Huang, and Lee (2018)
Nanoemulsion	Curcumin	Cervical carcinoma cell	2–40 μM curcumin, blue light (447 nm, 209 mW/cm^2, 80 J/cm^2)	≈10–100%	≈2%	Increase the activities of caspase-3/caspase-7	de Matos et al. (2018)
Ion pairing nanoparticles	Methylene blue and curcumin	MDA-MB-231 cancer cells	0–75 μg/ml curcumin, blue light (465 nm, 34 mW/cm^2)	≈100%	≈38%	Produce singlet oxygen	Hosseinzadeh and Khorsandi (2017)
Layered double hydroxide nanohybrid	Curcumin	MDA-MB-123 human breast cancer cell line	25 μg/ml curcumin, blue light (465 nm, 34 mW/cm^2)	≈90%	≈58%	Curcumin–LDH nanohybrids have higher photodynamic activity than free curcumin	Khorsandi et al. (2015)
NIR-controlled cage mimicking system	Curcumin	4T1 cells and 4T1 tumor-bearing mice	10–100 μg/ml curcumin, NIR laser (20 min, 3 mW/cm^2)	≈50–82%	≈15–70%	NIR irradiated nanosystem can recover the bioavailability of curcumin and increase ROS generation	Liu et al. (2017)
Hexagonal nanoparticles	Curcumin	Bel-7402 cells, SKOV-3 ovarian cancer cells, and MCF-7 cells	1000 μg/ml curcumin, NIR laser (980 nm,10 min, 0.5 mW/cm^2)	≈90%	≈20–40%	This drug delivery system can efficiently deliver curcumin to cancer cells to generate ROS upon the excitation of near-infrared light, so as to kill tumor cells.	Xiong, Sun, Gao, Li, and Duan (2016)
Curcumin nanoparticles	Curcumin	U251 glioma, B16 melanoma, and H460 lung cancer cells	10 μg/ml curcumin, blue light (465–475 nm, 1–8 min)	–	≈10%	Photoexcited nanocurcumin induces phosphorylation of c-Jun N-terminal kinase (JNK), mitochondrial depolarization, caspase-3 activation, and cleavage of poly (ADP-ribose) polymerase	Paunovic et al. (2016)
Curcumin organically modified silica nanoparticle complexes	Curcumin	Human squamous cell carcinoma cell line	25 μM curcumin, blue light (420 nm, 36 mW/cm^2, 20 J/cm^2)	≈50–85%	≈10–50%	Produce more ROS and inhibited the growth and migration of cells	Singh, Sharma, and Gupta (2015)
Organically modified silica nanoparticles	Curcumin	Human oral cancer cells	25 μM curcumin, light (400–700 nm, 200 mW/cm^2, 12, 20 J/cm^2)	≈52%	≈20%	Inhibit NF-κB activity, suppress NF-κB-regulated proteins involved in invasion (MMP-9), angiogenesis (VEGF), and inflammation (TNF-α)	Singh, Sharma, and Gupta (2014)

Ferrocenyl-terpyridine oxovanadium (IV) complexes of curcuminoids were used to treat HeLa and HepG2 cancer cells and proved able to induce nuclear morphological changes and cell apoptosis. Additionally, the complexes of curcuminoids in red light showed significant cleavage of supercoiled pUC19 DNA, while the control did not show any significant DNA cleavage activity (Balaji, Balakrishnan, Perumalla, Karande, & Chakravarty, 2014). Oxidovanadium (IV) complexes of curcumin exhibited selective mitochondrial localization and remarkable photo-cytotoxicity towards HeLa, HaCaT, and MCF-7 cancer cells, but were less toxic against 3T3 normal cells (Banerjee, Dixit, Karande, & Chakravarty, 2015; Banerjee et al., 2014; Prasad, Pant, Khan, Kondaiah, & Chakravarty, 2014). Di-iodinated boron-dipyrromethene appended copper (II) complexes of curcumin also exhibited mitochondria-targeted photo-cytotoxicity. In addition, cobalt (III) chaperone complexes of curcumin exhibited 20-fold greater photo-cytotoxicity than curcumin alone (Renfrew, Bryce, & Hambley, 2015) and were non-toxic to normal cells (Sarkar, Banerjee, & Hussain, 2015). Similarly, ternary cobalt (III) complexes of curcumin and mitocurcumin displayed 12-fold greater cytotoxicity under light irradiation than in dark (Garai et al., 2016). Sarkar, Butcher, Banerjee, Mukherjee, and Hussain (2016) synthesized dinuclear iron (III) complex of curcumin, which also had promising photo-cytotoxicity and negligible dark toxicity in cancer cells.

4. Antimicrobial and anticancer activities of curcumin-NPs-PDT

4.1. Antimicrobial activity of curcumin-NPs-PDT

Encapsulating curcumin in drug delivery systems is an alternative strategy to increase its bioavailability, such as encapsulation in nanoparticles, nanoemulsions, or cyclodextrins (Table 3). Gutierrez et al. (2017) encapsulated curcumin in polymeric nanoparticles for PDT against planktonic culture and biofilms of *S. mutans*, *C. albicans*, and Methicillin-resistant *S. aureus*. They found that the synthesized formulations improved the water solubility of curcumin and showed higher antimicrobial photodynamic effect on planktonic cultures than on biofilms. They also found that cationic curcumin-NPs exhibited stronger antimicrobial effect than anionic formulations, indicating that an antimicrobial PS should have pronounced cationic charges, especially when targeting Gram-negative bacteria. Pietra et al. (2017) also encapsulated curcumin in polymeric nanoparticles to improve its bioavailability. They reported that this nanoparticle could prevent the degradation of curcumin and eliminate some microorganisms, such as *C. albicans*, *Cryptococcus neoformans (C. neoformans)*, and *S. epidermidis*, at micromolar concentrations of curcumin.

Microemulsion consisting of Tween 80, propylene glycol, water, and geraniol, could homogeneously disperse and stabilize curcumin. Liu, Lee, and Wu (2016) applied this curcumin microemulsion for the photoinactivation of *Pseudomonas aeruginosa (P. aeruginosa)*. They found that this microemulsion could retain curcumin in the stratum corneum without damaging dermal tissue, and showed increased inhibition of *P. aeruginosa*, which is completely eliminated by a combination of EDTA and curcumin microemulsion under light-irradiation (455 nm, 16 mM/cm^2, 12 cm distance between the light and culture plate, 15 min, 14.4 J/cm^2).

Developing self-decontaminating antimicrobial surfaces is attracting increasing interest, especially those developed with natural photosensitive dyes such as curcumin. Shlar, Droby, and Rodov (2018) developed an antimicrobial coating based on curcumin-cyclodextrin complex, which showed bactericidal activity against *E. coli* in dark, and this activity was further enhanced by PDT. Therefore, this antimicrobial coating can be applied to control microbial contamination and transmission. Tosati, de Oliveira, Oliveira, Nitin, and Monteiro (2018) developed another type of turmeric residue edible coating to prevent cross-contamination of *L. innocua* on sausages. These coatings consisted of turmeric residue and either gelatin hydrogels or cassava starch. The gelatin hydrogels with purified curcumin could inactivate more than 5 log CFU/mL of *L. innocua* after light treatment with light irradiation conditions as follows: UV-A light source (320–400 nm, 18 W), 8 cm distance between sample and lamps, 32 W/m^2 light intensity, and 5 min.

In addition, other nanoparticles have been used to encapsulate curcumin to enhance its bioavailability. Kuthati et al. (2017) designed copper-impregnated mesoporous silica nanoparticles with immobilized silver nanoparticles to encapsulate curcumin for photodynamic inactivation of antibiotic-resistant *E. coli*. This curcumin-NP could improve the generation of ROS under light irradiation and then induce microbial death. Moreover, the surface of the nanoparticles was modified with a positive charge, which promoted an antimicrobial reaction to the negatively charged microbial cell membrane by electrostatic attraction. Other nanoparticles such as curcumin solid dispersions with methyl-β-cyclodextrin and hyaluronic acid (HA), hydroxypropyl methylcellulose (HPMC) or both HA and HPMC, were also prepared against *E. coli*, and successfully reduced colony-forming units (Wikene, Hegge, Bruzell, & Tonnesen, 2015).

4.2. Anticancer activity of curcumin-NPs-PDT

Curcumin-NPs have been shown to provide a solution to the critical limitation of natural curcumin, poor solubility and hydrolytic instability (Jiang et al., 2017). Nanoparticles can enhance the solubility of curcumin thereby increasing its cellular internalization. They can also improve the target specificity of curcumin by passively targeting tumor tissue, and enhancing permeability and retention effects. Moreover, cell-specificity of curcumin can be enhanced by modifying nanoparticle surface to bind active targeting moieties. Combination of these curcumin nanoformulations with PDT has been widely investigated to enhance photodynamic therapy. These merits are shown in Table 4.

Jiang et al. (2017) encapsulated curcumin into solid lipid nanoparticles (SLNs) to improve its therapeutic effect on A549 lung cancer cells. The results showed that curcumin-SLNs exhibited about 2.27-fold greater photo-cytotoxicity than free curcumin and induced cell cycle arrest at G2/M phase. In addition, these curcumin-SLNs could effectively deliver curcumin to mitochondria and produce more ROS, thereby increasing the expression of caspase-3 and caspase-9, promoting the ratio of Bax/Bcl-2, and disrupting mitochondrial membrane. Yu et al. (2017) developed polydopamine (PDA) nanoparticles with polyethylene glycol (PEG) modification, which was used to deliver photosensitizer chlorine6 (Ce6) and curcumin for combined PDT and radiotherapy (RT) of lung cancer. Combined PDT with RT based on PDA-PEG/curcumin/Ce6 nanoparticles remarkably inhibited the growth of cancer cells *in vitro*. In addition, the authors further confirmed this result *in vivo* using female Balb/c mice bearing A549 tumor as an animal model. They found that X-ray and laser irradiation of intratumorally injected PDA-PEG/Cur/Ce6 in mice significantly inhibited the growth of A549 tumors without significant side effects on major organs. These results indicate that this nanoparticle formulation combined with RT and PDT exhibited superior therapeutic performance. This result also inspired combined approaches that integrate the additive, synergistic, and complementary interactions between different treatments. Zhang et al. (2015) applied this concept to realize the design of self-monitoring and self-delivery of photosensitizer-doped nanoparticles for the treatment of lung cancer. During preparation, a donor/acceptor pair of perylene and 5, 10, 15, 20-tetro (4-pyridyl) porphyrin (H_2TPyP) is co-doped into curcumin matrix. H_2TPyP could emit red fluorescence and curcumin can emit green fluorescence. The green fluorescence was quenched (OFF) in the form of nanoparticles and could be subsequently recovered (ON) upon releasing curcumin in tumor cells. Thus, these nanoparticles provided a real-time dual-fluorescence imaging/tracking system *in vitro* and *in vivo*. In addition, these nanoparticles exhibited high cancer therapeutic efficiency both *in vitro* and *in vivo*.

Curcumin-NPs are frequently applied in PDT for the treatment of

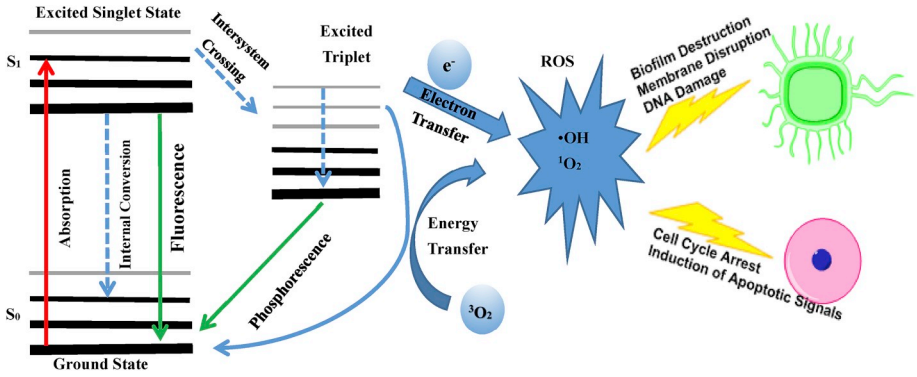

Fig. 2. Mechanisms of photodynamic therapy and curcumin photodynamic therapy. When a ground state PS absorbs light energy, it transfers into its excited singlet state. This excited state easily loses energy by emitting fluorescence from internal conversion and then returns to the ground state. The excited singlet state PS can transfer to its long-lived excited triplet state through intersystem crossing. This long-lived excited triplet state PS can generate ROS in the presence of molecular oxygen through electron or energy transfer reaction. The curcumin-PDT can damage microorganisms in four ways (biofilm destruction, membrane disruption, DNA damage, and generation of ROS) and induce cell apoptosis by two pathways (inhibition of cancer cell growth and induction of cancer cell apoptosis.

human breast cancer. Khorsandi, Hosseinzadeh, and Fateh (2015) intercalated curcumin into layered double hydroxide (LDH) for photodynamic therapy against human breast cancer cells. Curcumin can be stabilized in the host interlayer, which can improve its water solubility and dispersity. Compared to free curcumin, curcumin-LDH exhibited higher photo-cytotoxicity, indicating that LDH is a good curcumin delivery vehicle for photodynamic therapy in the treatment of breast cancer. In addition, complexation of curcumin-nanoparticles with other photosensitizing compounds has been widely investigated to enhance the efficacy of curcumin-NPs. Hosseinzadeh and Khorsandi (2017) used methylene blue-curcumin ion pair nanoparticles as photosensitizers in PDT for the treatment of breast cancer. Methylene blue-curcumin ion pair nanoparticles enhanced the cell penetration and photo-cytotoxicity of both dyes. Compared to blue light LED, red light LED had superior effect in activating both dyes to generate singlet oxygen, indicating that the light source also has an effect on PDT efficiency. Liu et al. (2017) developed an NIR-controlled cage mimicking system for the treatment of 4T1 tumor. They encapsulate curcumin inside the channels of the nanocarrier and released curcumin via NIR irradiation-triggered hydrophobicity-hydrophilicity switch of the spiropyran molecules. This system can significantly enhance antitumor efficiency *in vitro* and *in vivo*.

Curcumin-NPs have also been applied to treat glioblastoma tumor cells. Dev, Srivastava, Choudhury, and Karmakar (2016) reported that even a low dose of curcumin loaded BSA nanoparticles could provide improved photo-cytotoxicity against glioblastoma stem cells. Jamali et al. (2018) modified the surface of curcumin-loaded PLGA nanoparticles with monoclonal antibody (MAb-CURCUMIN-PLGA NPs) for the targeted phototherapy of human glioblastoma cell line. This study showed that MAb-CURCUMIN-PLGA NPs had higher photodynamic toxicity on the DKMG/EGFRvIII cells than CURCUMIN-PLGA NPs, indicating that the MAb-CURCUMIN-PLGA NPs are a well-targeted drug delivery system for PDT in EGFRvIII overexpressed tumor cells. Paunovic et al. (2016) investigated the *in vitro* anticancer effect of blue light-irradiated curcumin nanoparticles using U251 glioma, B16 melanoma, and H469 lung cancer cells as targets. Photoexcited nanocurcumin induced phosphorylation of c-Jun N-terminal kinase, mitochondrial depolarization, caspase-3 activation, and cleavage of poly (ADP-ribose) polymerase, causing apoptotic cell death.

Attempts have been made to combine anticancer drugs with curcumin-NPs for synergistic anticancer effects in PDT (Rajiu, Balaji, Sheena, Akbarsha, & Jeganathan, 2015). The cytotoxic effects of the anticancer drug, doxorubicin, and curcumin on human hepatocellular carcinoma cell lines were evaluated in nanoparticle forms. The combination of doxorubicin-conjugated curcumin-NPs enhanced photo-cytotoxic effect on HepG2 cells via ROS-mediated p53-dependent apoptotic pathway, and was a promising anticancer agent. Curcumin was also encapsulated into nanoliposomes and polyvinyl pyrrolidone-capped gold nanoparticles for the treatment of HepG2 cancer cells and Erlich solid tumor model. The cytotoxicity and antitumor effect of both curcumin-NPs were augmented by light irradiation, and the former nanoformulation was more cytotoxic than the latter (Fadel, Kassab, Abd El Fadeel, Nasr, & El Ghoubary, 2018).

Curcumin-NPs were also applied for the photodynamic treatment of other types of cancer cells such as gastric cancer, cervical carcinoma, human SKOV-3 ovarian cancer, B16 melanoma, human squamous cell carcinoma, CT-26, and human oral cancer cells (Table 4). All these nanoparticles enhance the curcumin accumulation in cells and enhance photo-cytotoxicity of curcumin towards diverse cancer cell lines.

5. Potential mechanism(s)

5.1. Mechanism of PDT

Three preconditions are required in PDT, including PS, light of appropriate wavelength, and oxygen dissolved in cells (Kwiatkowski et al., 2018) (Fig. 2). When PS absorbs light energy (*hv*), it will convert from ground state (S_0) into high energy excited singlet state (S_1), which is very unstable and easily loses energy and decays back to ground state by emitting fluorescence or by producing heat (internal conversion). In addition, the excited singlet state may undergo a process called 'intersystem crossing' to form a long-lived excited triplet state (T_1), which is more stable than S_1. PS molecule at T_1 can decay back to ground state via three possible ways. One way is by emitting phosphorescence, which is a 'forbidden process' because of the quantum selection rules. The second way is by transferring energy to molecular oxygen ($^3O_2$) to form singlet oxygen ($^1O_2$) and ground-state PS. The third way is to form free radicals and anion radicals of the PS by transferring hydrogen or electron. The singlet oxygen and radical anion can react with oxygen to produce ROS, which can damage most types of biomolecules including amino acids, lipids, and nucleic acids, thereby inducing cell death and necrosis in proximal tissues.

5.2. Mechanisms of antimicrobial action of photo-triggered curcumin

As described above, with regard to the PDT mechanism, ROS induces fatal damage to target cells and tissues, which is the main antimicrobial mechanism of curcumin-PDT. Jiang et al. (2014) highlighted that light-activated curcumin significantly increased the amount of ROS in *S. aureus* and caused significant structural damage to the membrane structure of *S. aureus,* thereby increasing its permeability and leading to significant intracellular substance leakage, leading cell death. Several studies even modified curcumin and encapsulated it in nanoparticles to achieve higher amounts of ROS under light irradiation. For example, Kuthati et al. (2017) demonstrated that curcumin in combination with copper-impregnated mesoporous silica nanoparticles and silver nanoparticles (SNP) could significantly ($p < 0.05$) enhance the generation of ROS under light irradiation through a synergistic mechanism of energy transfer of the absorbed light from SNP to curcumin. Baltazar et al. (2015) reported that encapsulation of curcumin in nanoparticles and

irradiation with blue light (417 nm, 10 J/cm^2, 17 min) could completely inhibit fungal growth by producing ROS and nitrogen species.

Increased ROS generation induces DNA damage, resulting in cell death. Carmello, Pavarina, Oliveira, and Johansson (2015) reported that DNA damage was noticeably observed after treatment with curcumin under blue light exposure, which may be due to the ROS generation. In addition, Hu et al. (2018) also reported that the use of curcumin as a photosensitizer to photo-inactivate *B. cepacia* caused obvious genomic DNA cleavage and induced large-scale degradation of protein due to ROS generation.

5.3. Mechanisms of anticancer activity of photo-triggered curcumin

5.3.1. Inhibition of cancer cell growth

The cell cycle of mammalian cells consists of four phases (G1, S, G2, and M), controlling cell growth and division. In G1 phase, cells grow and chromosomes prepare for replication. In S phase, DNA replicates and chromosomes duplicate. In G2 phase, the cell 'double checks' the duplicated chromosomes for error and makes any necessary repair. In M phase (mitosis), nuclear and cytoplasmic division occurs, producing two daughter cells. Several studies found that curcumin-NPs-PDT could inhibit the growth of cancer cells. Jiang et al. (2017) reported that encapsulated curcumin in solid-lipid nanoparticles could enhance photo-cytotoxicity towards A549 lung cancer cells at a low concentration of 1.5 μM curcumin and induce cell cycle arrest at G2/M phases, leading to cell death. Rajiu et al. (2015) treated HepG2 cells with curcumin nanoparticles and doxorubicin-anchored curcumin nanoparticles, and found that there was an increase in the percentage of cells in G2/M phase and S phase, respectively. This pattern of cell cycle arrest is highly associated with DNA fragmentation. In addition, photoactivated curcumin can also induce cell cycle arrest at G0/G1 (Kuang et al., 2012) and G2/M phases in MGC-803 human gastric cancer cells (Chen, Su, & Ma, 2000). Photoactivated curcumin may inhibit the expression of several major cell-cycle proteins and cyclin-dependent kinases (Deng, Verron, & Rohanizadeh, 2016).

5.3.2. Induction of cancer cell apoptosis

Apoptosis, also known as programmed cell death, is the genetic guiding process for cell self-destruction and is a normal physiological process in eliminating unwanted cells within the body. Apoptosis is marked by membrane blebbing, nuclear condensation and fragmentation of nuclear DNA. Deregulated apoptosis is the major reason for cancer development and progression. Curcumin-PDT can target apoptotic mechanisms in cancer cells leading to cancer cell death. Metal-bound complexes of curcumin such as boron-dipyrromethene (BODIY) appended copper (II) complexes of curcumin, oxovanadium (IV)-BODIPY conjugates of curcumin, ferrocenyl-terpyridine oxovanadium (IV) complexes of curcuminoids, oxidovanadium (IV) complexes of curcumin, and (acridinyl) dipyridophenazine oxidovanadium (IV) complexes of curcumin (Table 2) can impart mitochondria-targeted photo-cytotoxicity towards various cancer cells. These metal-bound complexes in combination with phototherapy induce the mitochondria-mediated apoptotic pathway in cancer cells with the formation of ROS. Activation of caspase family proteins also plays a key role in the process of apoptosis. Kuang et al. (2012) reported that photoactivated curcumin could significantly activate caspase-3, caspase-8, and caspase-9, and enhance the release of cytochrome C in MGC-803 cells. Curcumin-PDT induced the apoptosis of HaCaT cells by the activation of caspase-8, caspase-3, and caspase-9, followed by releasing cytochrome C (Park & Lee, 2007). The apoptosis of HaCaT cells treated with demethoxycurcumin in combination with PDT was triggered through activation of p53 and caspase pathways, and through upregulation of Bax and p-p65 expression and downregulation of Bcl-2, Mcl-1, and nuclear factor-κB expression (Xin et al., 2017).

6. Conclusions and perspectives

The application of curcumin as an antimicrobial and anticancer agent is hampered due to its instability and poor bioavailability. PDT combined with nanosystems is an attractive strategy to overcome these limitations of curcumin. Photo-triggered curcumin and curcumin-NPs have shown improved antimicrobial and anticancer activities. The major factors that determine the effectiveness of curcumin-PDT are curcumin concentration, nature of curcumin (free or complexed with metals), treatment time with curcumin, source, exposure time and doses of light. As a photosensitizer, the absorption wavelength of curcumin is about 450 nm (blue light). Because of the lower penetration ability of blue light into tissues, the use of curcumin-PDT is limited only to superficial skincare treatment. As a safety approach curcumin-PDT can be used to suppress the growth of microorganisms involved directly with dental decay and periodontitis, and some foodborne contaminations.

Although curcumin formulations exhibit promising photodynamic therapeutic effects on microbes and cancer *in vitro*, very few *in vivo* studies have been conducted. More studies are required on preclinical evaluation of photodynamic treatment with different curcumin formulations for antimicrobial and anticancer applications. This is very much essential for the translation of curcumin-PDT development to clinical practice. Besides, a lack of sufficient understanding of the photodegradation of curcumin has largely prevented researchers from modifying the curcumin structure to enhance its phototherapeutic potential. In addition, as a dietary spice, the photosensitivity of curcumin is weaker than some chemically synthesized photosensitizers. However, chemically synthesized photosensitizers may have greater potential health hazards than natural curcumin. Therefore, modifying curcumin structure with other natural compounds can improve its photosensitivity without increasing the toxicity.

Author contributions

H. C. conceived the idea, Q. Q. Y. drafted the manuscript, A. K. F., G. K., K. G., R. Y. G., and H. C. edited and revised the manuscript.

Declaration of competing interest

None.

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