

Antimicrobial Activity of Curcumin

Subjects: **Microbiology**

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Curcumin (CUR) is a natural substance extracted from turmeric that has antimicrobial properties. Due to its ability to absorb light in the blue spectrum, CUR is also used as a photosensitizer (PS) in antimicrobial Photodynamic Therapy (aPDT).

curcumin

drug delivery systems

antimicrobial agents

microbial drug resistance

viruses

bacteria

fungi

photochemotherapy

1. Introduction

The global changes arising from globalization and climate change have a profound impact on human health, including infectious diseases [1][2]. The increased mobility of people, urbanization, greenhouse-gas emissions, pollution, deforestation, global warming, loss of sea ice, sea-level rise, extreme weather events with droughts and flood, etc., have all contributed to affect the transmission, prevalence, and spread of existing infections, such as vector-borne diseases, and the emergence of new pathogens [1][2]. In some cases, these infections have resulted in epidemics such as dengue and pandemics such as COVID-19, which the world is currently facing [3].

Notwithstanding the existence of anti-infective medications, other current concerns are the drug resistance arising from the misuse of antimicrobial agents and the emergence of multidrug-resistant species [4]. These problems are a challenge for humanity, especially when considering that the development of new drugs demands time and money. Thus, the repurposing of existing medications and alternative therapies, such as natural substances, has been investigated [5][6][7].

Curcumin (CUR) is a yellow dye (diferuloylmethane—a natural polyphenol) found in turmeric (*Curcuma longa*), which is a plant native to India and Southeast Asia. Beyond its culinary use as food flavoring and coloring, CUR also has a potential application in medicine due to its therapeutic properties, which include antioxidant, anticancer, anti-inflammatory, and antimicrobial effects [8]. CUR is not toxic and, according to the Food and Drug Administration, it is “Generally Recognized as Safe” [9]. The literature shows a plethora of studies reporting the biological and pharmacological features of CUR on health. Comprehensive reviews are available on the anticancer [10], anti-inflammatory [8], and antimicrobial [11] effects of CUR.

Nonetheless, CUR is not soluble in water, unstable in solutions, and shows low bioavailability, poor absorption, and rapid elimination from the body [11]. For these reasons, organic solvents such as ethanol, methanol, acetone, and dimethyl sulfoxide (DMSO) have been used to solubilize CUR [12]. These drawbacks hinder the *in vivo* use of CUR

as a therapeutic agent. Thus, some approaches have been used to overcome the problems of CUR, such as the use of adjuvants and drug delivery systems. Piperine, a substance derived from black pepper, and lecithin, a phospholipid, have been associated with CUR to improve its bioavailability by blocking the metabolism of CUR and enhancing its gastrointestinal absorption [11]. Additionally, drug delivery systems have been used to solubilize CUR and protect it from degradation until it reaches the target tissue, where CUR is sustainably released [13].

Nanotechnology has been a promising field in medicine (nanomedicine). Nanoscale structures show intrinsic physical and chemical properties, which have been exploited as diagnostic and therapeutic tools [13][14]. The present study reviews the drug delivery systems (DDS) used for CUR, aiming at its antimicrobial effect. Although comprehensive reviews about the antimicrobial effect of CUR (encapsulated or not) are found elsewhere [15][16][17][18], they describe only the antibacterial and antifungal activities of CUR in DDSs. Our review summarizes the DDSs used for CUR as an antiviral, antibacterial, and antifungal agent, encompassing different nanosystems (colloids and metals) and the relevant issues of antimicrobial resistance and the emergence of new pathogens.

2. Free CUR

The broad-spectrum activity of CUR as an antibacterial, antifungal, and antivirus agent was reviewed previously [15][16]. Thus, this section reviews recent studies not covered by these reviews about the antimicrobial activity of free (non-encapsulated) CUR (**Table 1**) before reporting the DDS used for CUR.

Table 1. In vitro and in vivo studies using free CUR and curcuminoids as antimicrobial.

| Solvent | Microorganism | Culture | Antimicrobial Method | CUR Concentration | Light/Ultrasonic Parameters | Reference |
|--|------------------|----------------|---------------------------------------|-------------------|-----------------------------|-----------|
| DMSO (0.4%) | ZIKV >DGEV | Cell infection | IC ₅₀ >IC ₉₀ | 5.62–16.57 μM | - | [19] |
| N/R | HPVA Tulane V | Cell infection | Viral survival | 0.015 mg/mL | - | [20] |
| N/R | KSPV | Infected cells | EC ₅₀ | Up to 6.68 μM | - | [21] |
| Aqueous <i>Piper nigrum</i> seed extract | SARS-CoV-2 | Cell infection | IC ₅₀ Plaque reduction | 0.4 μg/mL | - | [22] |
| DMSO (<0.4%) | SARS-CoV-1 | Cell infection | Inhibiton of viral replication | 20 μM | - | [23] |

| Solvent | Microorganism | Culture | Antimicrobial Method | CUR Concentration | Light/Ultrasonic Parameters | Reference |
|-----------------|------------------------------------|--------------------------------|------------------------|-----------------------------|--|-----------|
| N/R | SARS-CoV | In vitro | Viral inhibition | 23.5 μ M | - | [24] |
| N/R | SARS-CoV | In vitro | papain-like inhibition | 5.7 μ M | - | [25] |
| DMSO (1 w/v) | <i>S. aureus</i> <i>E. coli</i> | Planktonic | Inhibition zone MIC | 600 and 400 μ g/mL | - | [26] |
| DMSO | MRSA | Planktonic | MIC FICI | 15.5 μ g/mL | - | [27] |
| S. aureus | | | | | | |
| N/R | MSSA | Planktonic | Colony count | 100 μ g/mL | 8 or 20 J/cm ² | [28] |
| MRSA | | | | | | |
| DMSO (10%) | <i>S. aureus</i> | Biofilm | aPDT | 20, 40, and 80 μ M | 5.28 J/cm ² | [29] |
| DMSO | VRSA | Biofilm/animal infection model | MIC MBC | 156.25 μ g/mL | 20 J/cm ² | [30] |
| N/R | <i>S. aureus</i> | Animal infection model | aPDT | 78 μ g/mL | 60 J/cm ² | [31] |
| DMSO | <i>S. aureus</i> | Infected fruit | Survival fraction | 100 nM | 1.5 and 9 J/cm ² | [32] |
| S. aureus | | | | | | |
| N/R | <i>E. coli</i> | Planktonic | PDI | 40 and 80 μ M | 15 J/cm ² | [33] |
| Tween 80 (0.5%) | <i>S. aureus</i> | Planktonic | CFU/mL | 300 and 500 μ M | 0.03–0.05 W/cm ² | [34] |
| N/R | <i>S. aureus</i> | Biofilm | Confocal microscope | N/R | 170 μ mol m ² s ¹ | [35] |
| DMSO (0.5%) | <i>S. aureus</i> | Biofilm | SDT aPDT SPDT | 80 μ M | 100 Hz 15 and 70 J/cm ² 100 Hz, 15 and 70 J/cm ² | [36] |
| DMSO | <i>E. coli</i> | Planktonic | MIC Inhibition zone | 110, 220 and 330 μ g/mL | - | [37] |

| Solvent | Microorganism | Culture | Antimicrobial Method | CUR Concentration | Light/Ultrasonic Parameters | Reference |
|----------------|--|-----------------------------------|----------------------|---------------------------------------|-----------------------------|-----------|
| DMSO | <i>E. coli</i> | Planktonic | OD _{600nm} | 8,16, 32, and 64 µg/mL | - | [38] |
| N/R | <i>S. dysenteriae</i> <i>C. jejuni</i> | Planktonic | MIC/MBC | 256 and 512 µg/mL | - | [39] |
| Edible alcohol | <i>E. coli</i> | Planktonic | aPDT | 5, 10, and 20 µM | 3.6 J/cm ² | [40] |
| DMSO | <i>H. pylori</i> | Planktonic biofilm | MIC MBC aPDT | 50 µg/mL | 10 mW/cm ² | [41] |
| DMSO | <i>P. aeruginosa</i> | Biofilm | aPDT CFU/mL | N/R | 5 and 10 J/cm ² | [42] |
| DMSO | Imipenem-resistant <i>A. baumannii</i> | Planktonic | aPDT | 25, 50, 100, and 200 µM | 5.4 J/cm ² | [43] |
| DMSO (2%) | <i>P. aeruginosa</i> , <i>A. baumannii</i> , <i>K. pneumoniae</i> , <i>E. coli</i> , <i>E. faecalis</i> | Planktonic | MIC/FICI | 128-256 µg/mL | - | [44] |
| N/R | <i>C. difficile</i> , <i>C. sticklandii</i> , <i>B. fragilis</i> , <i>P. bryantii</i> | Planktonic | Viable cell number | 10 µg/mL | - | [45] |
| N/R | <i>B. subtilis</i> , <i>E. coli</i> , <i>S. carnosus</i> , <i>M. smegmatis</i> | Planktonic | MIC/MBC | Up to 25 µM | - | [46] |
| N/R | MRSA <i>MSSA</i> <i>E. coli</i> | Planktonic/animal infection model | MIC | 4-16 µg/mL 2-8 µg/mL 8-32 µg/mL | - | [47] |
| N/R | <i>E. faecalis</i> , <i>S. aureus</i> , <i>B. subtilis</i> , <i>P. aeruginosa</i> , <i>E. coli</i> | Planktonic | MIC | 156 µg/mL | - | [48] |
| DMSO (0.5%) | <i>A. hydrophila</i> , <i>E. coli</i> , <i>E. faecalis</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>C. albicans</i> | Planktonic | MIC/MBC/FICI/aPDT | 37.5-150 µg/mL | N/C | [49] |
| N/R | <i>E. faecalis</i> | Infection model | CFU/mL | 1 µg/mL | - | [50] |

| Solvent | Microorganism | Culture | Antimicrobial Method | CUR Concentration | Light/Ultrasonic Parameters | Reference | |
|-----------------------------|--|---------------------|----------------------|-------------------|-------------------------------|-----------|------|
| Commercial solution | <i>E. faecalis</i> | Biofilm | aPDT | 1.5 g/mL | 20.1 J/cm ² | [51] | |
| Ethanol 99% | <i>A. hydrophila</i> , <i>V. parahaemolyticus</i> | Planktonic | aPDT/SDT | Up to 15 mg/L | N/C | [52] | |
| DMSO (10%) | <i>E. faecalis</i> | Biofilm | MIC/MBC | 120 mg/mL | - | [53] | |
| N/R | <i>S. mutans</i> | Planktonic | aPDT | 10 g/100cc | N/C | [54] | |
| DMSO: ethyl alcohol | <i>S. mutans</i> , <i>S. pyogenes</i> | Planktonic | aPDT | 3 mg/mL | 28.8 J/cm ² | [55] | |
| DMSO (0.8%) | Caries isolated | Biofilm | aPDT | 600 µg/mL | 75 J/cm ² | [56] | |
| DMSO | <i>S. mutans</i> , <i>C. albicans</i> | Biofilm single/dual | MBEC | 0.5 mM | - | [57] | |
| DMSO (0.05 M) | <i>A. actinomycetemcomitans</i> | Planktonic | aPDT | 40 µg/mL | 300–420 J/cm ² | [58] | |
| DMSO (<1%) | <i>P. gingivalis</i> , <i>A. actinomycetemcomitans</i> | Planktonic | aPDT | 20 µg/mL | 6, 12 or 18 J/cm ² | [59] | |
| DMSO (0.5%) | <i>P. gingivalis</i> , <i>A. actinomycetemcomitans</i> , <i>C. rectus</i> , <i>E. corrodens</i> , <i>F. nucleatum</i> , <i>P. intermedia</i> , <i>P. micra</i> , <i>T. denticola</i> , <i>T. forsythia</i> | Biofilm | aPDT | 100 mg/L | - | [60] | |
| N/R | Subgingival plaque | Biofilm | aPDT | 100 µg/mL | 30 J/cm ² | [61] | |
| DMSO | <i>P. gingivalis</i> | Plankton | [61][73][74] | MIC | 12.5 µg/mL | - | [62] |
| Ethanol: DMSO (99.9%: 0.1%) | Periodontal pocket | - | aPDT | 100 mg/mL | 7.69 J/cm ² | [63] | |
| [11][73][74] | | | | | | | |
| Tween 80 | <i>Streptococcus</i> spp., <i>Staphylococcus</i> spp., <i>Enterobacteriaceae</i> , <i>C. albicans</i> | Clinical trial | aPDT | 0.75 mg/mL | 20.1 J/cm ² | [19][64] | |
| | | [19] | | | | | |
| Sodium hydroxide: | <i>C. albicans</i> , <i>C. parapsilosis</i> , <i>C.</i> | Planktonic/biofilm | MIC | 0.1–0.5 mg/mL | - | [65] | |

Surrogate of the human norovirus, [20]. CUR was able to inhibit the viral replication of Kaposi's sarcoma-associated herpesvirus (KSHV) as well as reduce its pathogenesis (neoangiogenesis and cell invasion of KSHV-infected mesenchymal stem cell from the periodontal ligament) [21].

While the antiviral effect of CUR has been experimentally demonstrated, the effect of CUR against the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of COVID-19, has been predicted by in silico studies using computational techniques, such as molecular docking [75][76][77][78][79][80][81][82]. These in silico studies showed the binding affinity of CUR to the spike protein of SARS-CoV-2 and the human receptors of the host cell, which could inhibit the viral infection into the human cells. The targets to which CUR may bind are the viral non-structural protein 9 (Nsp9) [77] and 15 (Nsp15) [81], main proteases of SARS-CoV-2 (important for viral

| Solvent | Microorganism | Culture | Antimicrobial Method | CUR Concentration | Light/Ultrasonic Parameters | Reference |
|-------------|--|------------------------------------|-----------------------|----------------------|---|-----------|
| PBS | <i>glabrata</i> , <i>C. dubliniensis</i> | [76][82] | | | | [79] |
| N/R | <i>C. albicans</i> , <i>S. aureus</i> | Planktonic Biofilm | MIC/Biofilm percentag | 200 µg/mL | - | [66] |
| N/R | <i>C. albican</i> [83] | Biofilm | aPDT | 1.5 g/mL | 20.1 J/cm ² | [67] |
| DMSO (10%) | <i>C. albicans</i> | Biofilm | aPDT | 20, 40, 60 and 80 µM | 2.64, 5.28, 7.92, 10.56, and 13.2 J/cm ² | [68] |
| DMSO (1%) | <i>C. albicans</i> | Biofilm | aPDT | 40 and 80 mM | 37.5 and 50 J/cm ² | [69] |
| N/R | <i>C. albicans</i> | Biofilm | aPDT | 100 µM | 10 J/cm ² | [70] |
| DMSO (2.5%) | Fluconazole-resistant <i>C. albicans</i> [23][24] | Planktonic/biofilm/infection model | MIC/ aPDT | 40 µM | 5.28 J/cm ² | [71] |
| | Fluconazole-susceptible <i>C. albicans</i> [24] | | | 80 µM | [23] 40.3 J/cm ² | |
| DMSO | <i>C. albicans</i> , <i>F. oxysporum</i> , <i>A. flavus</i> , <i>A. niger</i> , <i>C. neoformans</i> | [25] Planktonic | MIC | 137.5–200 µg/mL | - | [72] |

2.2. Antibacterial Activity

The antibacterial effect of CUR has been demonstrated against Gram-positive and Gram-negative species, including strains responsible for human infections and showing antibiotic resistance [11][16][85][86]. CUR also inhibits bacterial biofilms, which are communities of cells embedded in a self-produced polymeric matrix tolerant to antimicrobial treatments [11][16][85][86]. The antibacterial mechanism of action of CUR involves damage to the cell wall or cell membrane, interference on cellular processes by targeting DNA and proteins, and inhibition of bacterial quorum sensing (communication process mediated by biochemical signals that regulate cell density and microbial behavior) [85]. Moreover, CUR affected the L-tryptophan metabolism in *Staphylococcus aureus* (Gram-positive) but not in *Escherichia coli* (Gram-negative), produced lipid peroxidation, and increased DNA fragmentation in both bacteria [26]. These results, along with the increased levels of total thiol and antioxidant capacity observed after bacterial cells were treated with CUR, suggested that oxidative stress may be the mechanism of antibacterial action of CUR [26]. Therefore, these multiple targets make CUR an interesting option for antibiotic-resistant strains. CUR is effective in killing methicillin-resistant *S. aureus* (MRSA), which is a concerning pathogen responsible for nosocomial and community-associated infections [86]. CUR and another polyphenol, quercetin, inhibited the growth of MRSA and their combination was synergistic [27]. Moreover, CUR absorbs blue light (400–500 nm) and is used as a natural photosensitizer (PS) in antimicrobial Photodynamic Therapy (aPDT) [87]. CUR-mediated aPDT reduced the viability of reference strain of *S. aureus* and clinical isolates of methicillin-sensitive *S. aureus* (MSSA) and MRSA by 4 log₁₀, while CUR alone reduced their survival by 2 log₁₀ [28]. The aPDT mediated by CUR in 10% DMSO reduced the biofilm viability of *S. aureus* and MRSA by 3 and 2 log₁₀, respectively, and their metabolic activity by 94% and 89%, respectively [29]. The antibiofilm activity of CUR-mediated aPDT was also observed against clinical isolates of vancomycin-resistant *S. aureus* (VRSA), with reductions of 3.05 log₁₀ in biofilm viability, 67.73% in biofilm biomass, and 47.94% in biofilm matrix [30]. Additionally, aPDT resulted in the eradication

of VRSA in a rat model of skin infection [30]. The association of CUR-mediated aPDT with artificial skin resulted in a $4.14 \log_{10}$ reduction in *S. aureus* from infected wounds in rats [31].

The combination of CUR and another natural PS, hypocrellin B, increased the photoinactivation of *S. aureus* compared with the photodynamic effect of each PS alone [32]. Bacterial cells showed alteration in their membrane integrity and the dual-PS-mediated aPDT also decontaminated apples with *S. aureus* [32]. The CUR-mediated aPDT was also effective in decontaminating food, reducing the number of *S. aureus* recovered from meat and fruit [33]. Compared to another natural PS, aloe-emodin, CUR was less effective in photokilling *S. aureus* and *E. coli* [34]. Three-dimensional cages fabricated with CUR and resin monomer (pentaerythritol triacrylate) polymerized by infrared light were used to entrap and kill *S. aureus*. Irradiation of cages for 10 min with visible light resulted in a bacteria mortality rate of 95% [35]. Following the principles of aPDT, Sonodynamic Therapy (SDT) associates a PS (also called sonosensitizer) with ultrasound (US) instead of light for the treatment of deeper lesions and infections, where light cannot reach [36]. Both aPDT and SDT mediated by CUR, as well as the combination of both (SPDT, when the PS is activated by light and US simultaneously), reduced the viability of *S. aureus* biofilms. SPDT promoted the highest reduction ($3.48 \log_{10}$), which was potentiated when CUR was combined with sodium dodecyl sulfate ($7.43 \log_{10}$) [36]. Regarding Gram-negative species, CUR alone was not able to inhibit the growth of an Enterotoxigenic *E. coli*, which is a strain that causes severe diarrhea and is resistant to antibiotics [37]. However, synergism was observed between CUR at $330 \mu\text{g/mL}$ and antibiotics (Ceftazidime, Amoxicillin/Clavulanic acid, Cefotaxime, and Ampicillin) [37]. CUR did not affect the growth of enteroaggregative (EAEC) and enteropathogenic (EPEC) diarrheagenic *E. coli* but inhibited the secretion and release of their virulence factors, *Pet*, and *EspC*, which are toxins produced by these strains [38]. Conversely, CUR alone and with ampicillin inhibited the growth of other species that caused diarrhea—*Shigella dysenteriae* and *Campylobacter jejuni*, including multidrug-resistant strains [39]. The aPDT mediated by CUR and light reduced the viability of *E. coli* by 3.5 log, increased membrane permeability of bacteria, and decontaminated oysters [40]. CUR-mediated aPDT reduced the viability of *Helicobacter pylori* and its virulence factors (motility, urease production, adhesion to erythrocytes, and biofilm formation) [41]. On *Pseudomonas aeruginosa*, aPDT potentiated the inhibitory effect of CUR, inhibited biofilm formation and matrix production, reduced biofilm thickness, and downregulated quorum sensing genes [42]. The photoinactivation of imipenem-resistant *Acinetobacter baumannii* reduced bacterial viability by 97.5% and shotgun proteomics analysis identified 70 carbonylated proteins modified after CUR mediated aPDT related to the membrane, translation, and response to oxidative stress [43]. CUR inhibited the growth of antibiotic-resistant *P. aeruginosa*, *A. baumannii*, and *Klebsiella pneumoniae* isolated from burn wound infections and showed synergism with meropenem [44]. On gastrointestinal bacteria of human and bovine origin, CUR inhibited Firmicutes (*Clostridioides difficile* and *Acetonaerobium (Clostridium) sticklandii*) but did not affect Bacteroidetes (*Bacteroides fragilis* and *Prevotella bryantii*) [45]. CUR was conjugated to triphenyl phosphonium resulting in a compound named Mitocurcumin, which inhibited the growth of *Bacillus subtilis*, *E. coli*, *Staphylococcus carnosus*, and *Mycobacterium smegmatis*, and induced morphological changes in *B. subtilis* [46]. Seventeen synthesized monocarbonyl curcuminoids showed high antibacterial activity against MSSA and MRSA and moderate activity against *E. coli* [47]. The four most effective curcuminoids were bacteriostatic at low concentrations and bactericidal at high concentrations against MRSA, which showed membrane damage. In an ex vivo mammalian co-culture infection model, two curcuminoids

decreased the viability of MSSA internalized in the fibroblasts [47]. One of thirteen synthesized curcuminoids, 3,30-dihydroxycurcumin, showed antibacterial activity against *S. aureus*, *B. subtilis*, *Enterococcus faecalis*, and *Mycobacterium tuberculosis*, and produced membrane damage on *B. subtilis* [48]. Nonetheless, all the synthesized curcuminoids were not effective against Gram-negative species (*P. aeruginosa* and *E. coli*) [48]. CUR analogs (monocurcuminoids, MC) were synthesized and showed higher, lower, or similar antimicrobial activity than CUR against *Aeromonas hydrophila*, *E. coli*, *E. faecalis*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, and the yeast *Candida albicans* [49]. Two MC and turmeric powder presented synergism against *A. hydrophila*, *P. aeruginosa*, and *C. albicans*. When aPDT was performed with UV light, two MC-mediated aPDT decreased the growth of *E. faecalis*, *E. coli*, and *S. aureus*, while aPDT with another MC and CUR increased the growth of *A. hydrophila*, *E. faecalis*, *S. aureus*, *C. albicans*, and *P. aeruginosa* [49]. CUR was more effective than other natural biomolecules (quercetin and resveratrol) in inhibiting the growth of *E. faecalis* in spermatozoa from rabbits, but less effective than antibiotics [50]. CUR-mediated aPDT also reduced the viability of *E. faecalis* biofilms grown in bovine bone cavities for 14 days by $1.92 \log_{10}$ [51]. The aPDT and the combination of a nanobubble solution and the US reduced the viability of the aquatic pathogens *Aeromonas hydrophila* and *Vibrio parahaemolyticus* [52].

CUR and aPDT have been used for dental infections and oral diseases. The *Curcuma longa* extract decreased the viability of 3-week-old *E. faecalis* biofilms formed on the root canal surface of human teeth [53]. The aPDT mediated by CUR and continuous laser irradiation eradicated planktonic cultures of *Streptococcus mutans*, which is the main etiologic factor of dental caries [54]. A formulation of syrup with curcuminoids and 30% sucrose was used as a PS in aPDT, which reduced the viability of *S. mutans*, *Streptococcus pyogenes*, and a clinical isolate from a patient with pharyngotonsillitis [55]. Microbial samples from carious dentin were grown as microcosm biofilm and submitted to CUR-mediated aPDT, which reduced the vitality of 3- and 5-day-old biofilms [56]. CUR alone decreased the biomass and the viability of mono- and dual-species biofilms of *S. mutans* and *C. albicans*, as well as the production of biofilm matrix and the expression of genes related to glucosyltransferase and quorum sensing of *S. mutans*, and the adherence of *C. albicans* [57]. The therapeutic effect of CUR on periodontal diseases was extensively investigated in animal models and clinical trials, which were reviewed [89]. Beyond its antibacterial activity, CUR-mediated aPDT also produced a bystander effect (behavior change of cells exposed to treated target cells) on the periodontal pathogen *Aggregatibacter actinomycetemcomitans*, reducing its survival, metabolic activity, and the production of quorum sensing molecule [58]. The aPDT with CUR decreased the growth of both *A. actinomycetemcomitans* and *Porphyromonas gingivalis*, which is another pathogenic periodontal bacterium [59]. Antimicrobial photothermal treatment promoted higher reduction than CUR-mediated aPDT in the viability of mixed biofilms of periodontal pathogens (*P. gingivalis*, *A. actinomycetemcomitans*, *Campylobacter rectus*, *Eikenella corrodens*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Parvimonas micra*, *Treponema denticola*, and *Tannerella forsythia*) grown on a titanium surface inside artificial periodontal pockets [60]. The aPDT mediated by different PS (methylene blue, CUR, and chlorin e6) eradicated the planktonic growth and reduced the biofilm viability of metronidazole-resistant bacteria from the subgingival plaque [61]. CUR alone inhibited the growth of *P. gingivalis* and CUR in gel was biocompatible when evaluated subcutaneously in rats [62].

A randomized clinical trial showed that CUR-mediated aPDT associated with scaling and root planing improved the clinical attachment level gain of periodontal pockets in type-2 diabetic patients after three and six months [63]. The

aPDT with CUR and LED applied in the mouth of 30 patients with acquired immune deficiency syndrome (AIDS) reduced the counts of *Streptococcus* spp., *Staphylococcus* spp., and total microorganisms from saliva, but not the number of Enterobacteriaceae and *Candida* spp. [64]. Additionally, there was no reduction in patients with CD8 lymphocytes lower than 25% [64].

2.3. Antifungal Activity

The antifungal activity of CUR has been demonstrated mostly against *Candida* spp. by many in vitro and few in vivo studies [90]. CUR inhibited the growth of a reference strain and a clinical isolate of *C. albicans*, as well as reference strains of *Candida parapsilosis*, *Candida glabrata*, and *Candida dubliniensis* [65]. When biofilms of both *C. albicans* strains were evaluated, CUR reduced only the viability of the standard strain in a concentration-dependent effect, while the antifungal fluconazole did not inhibit the viability of either strain [65]. CUR and 2-aminobenzimidazole (2-ABI) inhibited the growth and adhesion of *C. albicans* and *S. aureus* to medical-grade silicone [66]. The combination of CUR and 2-ABI enhanced the inhibition of biofilm formation and reduced the viability of 48 h-old single and dual-species biofilms [66]. The aPDT mediated by CUR reduced the survival of 14-day-old biofilm of *C. albicans* in bone cavities, confirmed by fluorescence spectroscopy [67]. CUR-mediated aPDT reduced the metabolic activity of biofilms of *C. albicans* reference strain and clinical isolates from the oral cavity of patients with HIV and lichen planus [68]. Moreover, genes related to hyphae and biofilm formation were downregulated [68]. The aPDT mediated by CUR and another PS, Photodithiazine®, also resulted in the downregulation of genes involved in adhesion and oxidative stress response in *C. albicans* biofilms [69]. CUR alone and CUR-mediated aPDT, combined or not with an antibody-derived killer decapeptide, reduced the metabolic activity of an 18 h biofilm of *C. albicans* [70]. CUR showed synergism with fluconazole and CUR-mediated aPDT inhibited the planktonic growth and reduced the biofilm viability of fluconazole-resistant *C. albicans* [71]. CUR-mediated aPDT also increased the survival of *Galleria mellonella* infected with fluconazole-susceptible *C. albicans*, but did not affect the survival of larvae infected with fluconazole-resistant strain [71]. A library of 2-chloroquinoline incorporated monocarbonyl curcuminoids (MACs) was synthesized and most of the MACs exhibited strong or moderate antifungal activity compared with miconazole against *C. albicans*, *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus niger*, and *Cryptococcus neoformans* [72]. To suggest a possible antifungal mechanism, a molecular docking analysis showed that MACs had binding affinity to sterol 14 α -demethylase (CYP51), leading to impaired fungal growth [72].

3. Curcumin in DDSs (Colloidal, Metal, and Hybrid Nanosystems)

3.1. CUR in Micelles

Micelles are aggregates of surfactants or block polymers self-assembled in water solution. They are used as DDSs and formed by a hydrophilic domain named corona and a hydrophobic domain called core (Figure 1) [91], which stays in contact with hydrophobic drugs such as CUR [91]. Micelles have low toxicity, biocompatibility, and

sustained release, which makes them an attractive DDS to carry CUR and to be used in medical applications [91]. Antimicrobial studies with CUR-loaded micelles are summarized in **Table 2**.

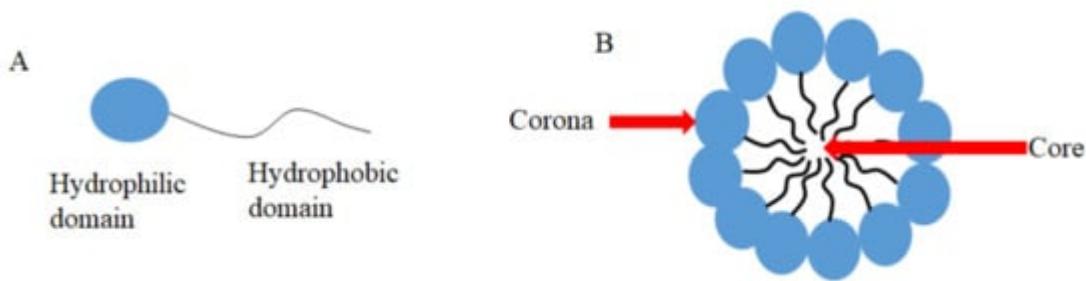


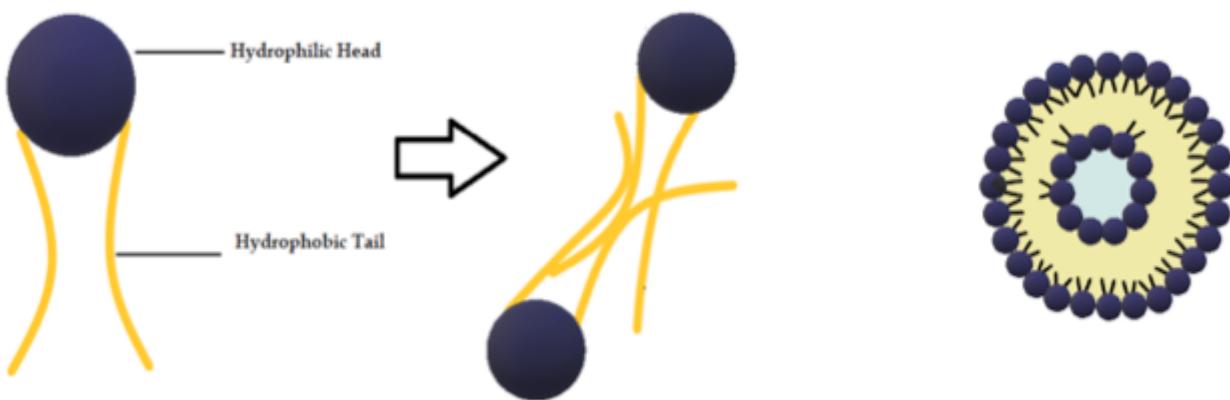
Figure 1. Schematic representation of: (A) an amphiphilic molecule and (B) an assembled micelle.

Table 2. Antimicrobial studies performed with CUR in micelles.

| Type of Micelles | [CUR] Formulation | Microorganism | Type of Culture | Antimicrobial Method | Antimicrobial [CUR] | Light/Ultrasonic Parameters | Reference |
|--|-------------------|---|--------------------|---------------------------------|---|-----------------------------|-----------|
| Mixed polymer micelles | 1000 ppm | <i>E. coli</i> , <i>S. aureus</i> , <i>A. niger</i> | Planktonic | MIC | 350 and 275 $\mu\text{g/mL}$ | - | [92] |
| PCL- <i>b</i> -PAsp and Ag | 2 mg/mL | <i>P. aeruginosa</i> , <i>S. aureus</i> | Planktonic | OD _{600nm} | 8–500 $\mu\text{g/mL}$ | - | [93] |
| mPEG-OA | 1:10 | <i>P. aeruginosa</i> | Planktonic | MIC | 400 $\mu\text{g/mL}$ | - | [94] |
| PEG-PCL | 10 mg | <i>C. albicans</i> | Planktonic | MIC | 256 $\mu\text{g/mL}$ | - | [95] |
| PEG-PE | 50 mM | <i>S. mutans</i> | Planktonic | SACT | 50 mM | 1.56 W/cm ² | [96] |
| DAPMA, SPD, SPM | 0.32 mg/mL | <i>P. aeruginosa</i> | Planktonic | OD _{600nm} and aPDT | 250, 500 nM, 1 μM and 50, 100 nM | 18 and 30 J/cm ² | [97] |
| P123 | 0.5% w/V | <i>S. aureus</i> | Planktonic | aPDT | 7.80 $\mu\text{mol/L}$ | 6.5 J/cm ² | [98] |
| PCL- <i>b</i> -PHMG- <i>b</i> -PCL, STES | 10 mg | <i>S. aureus</i> , <i>E. coli</i> | Planktonic | MIC | 16 and 32 $\mu\text{g/mL}$ * | - | [99] |
| CUR-PLGA-DEX | 1 mg/mL | <i>P. fluorescens</i> , <i>P. putida</i> | Planktonic biofilm | OD _{600nm} antibiofilm | 0.625–5 mg/mL | - | [100] |

3.2. CUR in Liposomes

Liposomes are biodegradable and biocompatible systems, which consist of hydrophobic and hydrophilic groups (Figure 2) [101]. The hydrophobic layer is mainly composed of phospholipids and cholesterol molecules. This lipid-based carrier is suitable for administering water-insoluble drugs, such as CUR [102]. Liposomes are classified into three groups: single unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles [103]. Drugs encapsulated in liposomes are protected from chemical degradation and show increased drug solubility [101]. Additionally, liposomes have advantageous properties such as better penetration into the skin, deposition, anti-melanoma, and antimicrobial activity [102]. Antimicrobial studies with CUR-loaded liposomes are summarized in Table 3.



Figure

3.11. CUR in Films, Hydrogels, and Other Nanomaterials

2. Schematic representation of the liposome structure.

Antimicrobial studies with CUR in films, hydrogels, and other nanomaterials are summarized in Table 11.

Table 3. Antimicrobial studies performed with CUR in liposomes and solid lipid nanoparticles (SLN).

| Table 11. Antimicrobial studies performed with CUR in films, hydrogels, and other nanomaterials. | | | | | | | | |
|--|-------------------|---|-----------------------------|---------------------------------------|-------------------|-----------------------------|---------------|------------|
| Type of Nanosomes or [CUR] | Microorganism | Type of | Antimicrobial | Antimicrobial | Antimicrobial | Antimicrobial | Antimicrobial | Preference |
| Type of Material | [CUR] Formulation | Microorganism | Type of Culture | Method | [CUR] | Light/Ultrasonic Parameters | Reference | |
| CuR-SiNPs | 20 mg | <i>S. aureus</i> , <i>P. aeruginosa</i> | Planktonic, Biofilm | aPDT | 50 µg/mL, 1 mg/mL | 20 J/cm ² | [210] | [104] |
| CUR-HNT-DX | 10 mg | <i>S. marcescens</i> , <i>E. coli</i> | Planktonic, Infection model | Grown inhibition, Confocal microscopy | Up to 0.5 mg/mL | - | [211] | |
| Exosomes | N/R | HIV-1 infection | - | Flow cytometry | N/R | - | [212] | [105] |
| Electrospun nanofibers | 100 mg/mL | <i>Actinomyces naeslundii</i> | Biofilm | aPDT | 2.5 and 5 mg/mL | 1200 mW/cm ² | [213] | |
| Ga NFCD-GO NF | 0.1 mol | <i>B. cereus</i> , <i>E. coli</i> | Planktonic | Zone of inhibition, MIC | Up to 63.25 µg/mL | - | [214] | [106] |
| PLGA: triglycerides: F68 | 0.8 mg/mL | <i>E. coli</i> , <i>S. typhimurium</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>B. sonorensis</i> | Planktonic | MIC | 75 and 100 µg/mL | | | [107] |

| | | | | | | | | |
|----------------------|--------------------------------|---|-----------------------------------|-----------------------------------|-------------------|---|-------|------------------------|
| Multinanofibers-film | 1, 2.5, and 5 mg/mL | <i>S. aureus</i> <i>E. coli</i> | Planktonic | UFC/mL, Confocal microscopy | 1 mg/mL | - | [215] | ference |
| Nanofibers scaffolds | 4.0 wt% | <i>S. aureus</i> <i>Pseudomonassp.</i> | Planktonic | Colony count | N/R | - | [216] | [104] |
| Nanofibrous scaffold | 5% | <i>S. aureus</i> , <i>E. coli</i> | Planktonic | Colony count | 20 mg | - | [217] | |
| Nanofibers | 5 and 10%wt | <i>S. aureus</i> <i>E. coli</i> | Planktonic | OD _{600nm} | Up to 212.5 µg/mL | - | [218] | |
| CSDG | 1 w/w | <i>S. aureus</i> , <i>E. coli</i> | Planktonic, Infection model | Colony count, Microscopy | N/R | - | [219] | [108] |
| Gelatin film | 0, 0.25, 0.5, 1.0, and 1.5 wt% | <i>E. coli</i> , <i>L. moncytogenes</i> | Planktonic | UFC/mL | 0.25 and 1.5 wt% | - | [220] | tant and |
| ZnO-CMC film | 0.5 and 1.0 wt% | <i>E. coli</i> , <i>L. moncytogenes</i> | Planktonic | UFC/mL | 1 wt% | - | [221] | CUR and |
| Pectin [220] | 40 mg | <i>E. coli</i> , <i>L. moncytogenes</i> | Planktonic | UFC/mL | N/R | - | [222] | resistant reatment, |
| Edible film | 0.4% (w/v) | <i>E. coli</i> , <i>B. subtilis</i> | Planktonic | Zone of inhibition | 1% wt. | - | [223] | to study rugs and |

avoiding over- or under-estimation of interactions. For example, while the time-kill curve of *C. jejuni* treated with

3.3. CUR in Solid Lipid Nanoparticles

both cinnamon oil and ZnO NPs resulted in the over-estimation of synergism between the antimicrobials, the fractional inhibitory concentration index (FICI) method showed no synergism but only an additive effect [225]. The Solid lipid nanoparticles (SLN, Figure 3, Table 3) are a modern type of lipid-based carrier composed by solid FICI method was not able to detect the synergism between binary combinations of antimicrobials (cinnamon oil, biodegradable lipids and spherical solid lipid particles. SLNs are water colloidal or aqueous surfactant solution ZnO NPs, and CUR encapsulated in starch) at sub-MIC, which resulted in the non-turbidity of *C. jejuni*. In turn, systems [102]. SLNs have advantages such as biocompatibility, biodegradability, greater drug absorption, and drug mathematical modeling using isobolograms and median-effect curves showed synergism when CUR in starch was retention [18][102], thus they are an interesting system to carry CUR [14]. Currently, SLNs have become popular combined with other antimicrobials against *C. jejuni*, with bacterial reductions of 3 log for the binary combination because they are used as carriers for COVID-19 vaccines based on RNA vaccine technology (Moderna and and over 8 log for the tertiary combination. The mathematical modeling suggested that CUR in starch was the main Pfizer–BioNTech). antimicrobial responsible for the synergistic interaction [225].

In addition to the antimicrobial evaluation, in vitro and in vivo studies have demonstrated the cytocompatibility and biocompatibility of CUR in DDSs [108][113][114][115][118][121][144][145][152][156][168][185][192][202][209], suggesting that CUR-loaded DDSs might be safe. Although a plethora of DDSs has been developed to circumvent the hydrophobicity, instability in solution, and low bioavailability of CUR, several studies are still performed with free CUR dissolved in organic solvents [19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][85][86][87][88][89][90]. Furthermore, compared to several in vitro investigations, few in vivo studies using animal infection models and scarce clinical trials have been reported. A randomized clinical trial showed that aPDT mediated by free CUR improved gingivitis in adolescents under fixed orthodontic treatment but did not reduce dental plaque accumulation after 1 month [226]. Clinical improvements after CUR-mediated aPDT were also observed for periodontal diseases, although few studies have evaluated the microbiological parameters [63][89]. Therefore, the improvement of clinical parameters might be due to the anti-

inflammatory effect of CUR/aPDT instead of their in vivo antimicrobial activity. Nonetheless, randomized clinical trials evaluating CUR in DDSs against infections are required.

As a note on the future use of CUR, the incorporation of CUR in DDS and other pharmaceutical formulations allows its clinical use especially as an adjuvant agent to conventional antimicrobial agents. Such a combination can be an important weapon in the battle against resistant strains and emergent pathogens. The use of stimuli-responsive (or smart) DDS can also improve CUR delivery and its therapeutic effect on the target tissue. The combination of polymeric and metallic carriers may also enhance the therapeutic activity of CUR. Nonetheless, the degradation of DDS and its clearance from the body are other issues that require further investigation [18]. The evidence produced so far about the antimicrobial activity of CUR in DDSs supports future in vivo and clinical studies, which may pave the way for industrial production.

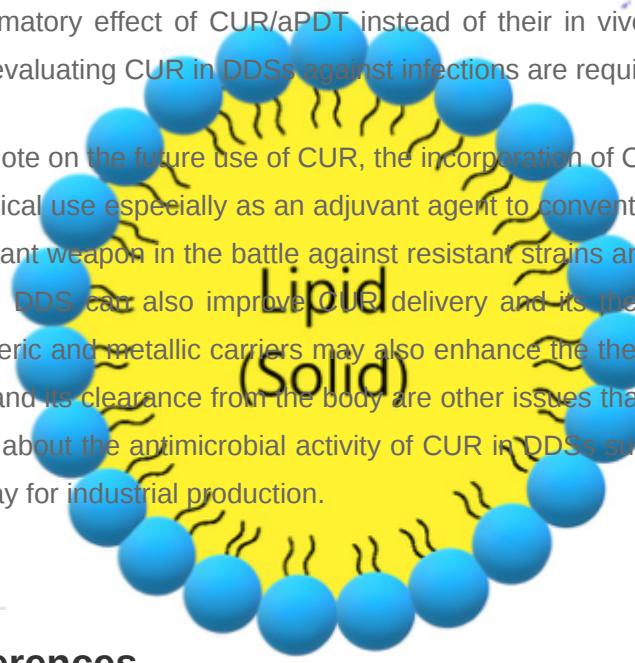


Figure 3. Schematic representation of solid lipid

References

nanoparticle.

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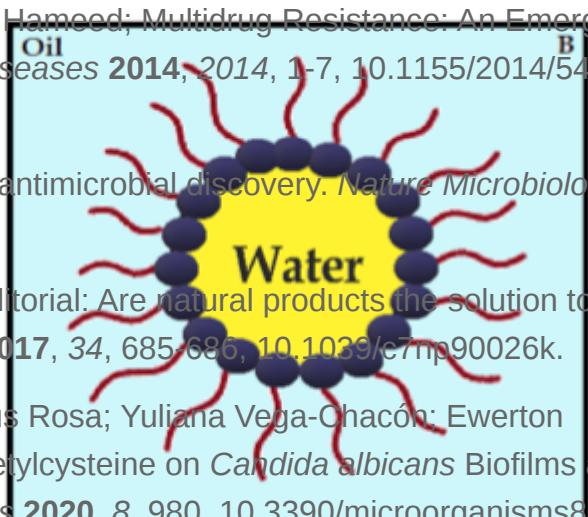


Figure 4. Schematic diagram of oil-in-water nanoemulsion (A) and water-in-oil nanoemulsion (B), stabilized by surfactants.

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| | Type of Emulsion | [CUR] Formulation | Microorganisms | Type of culture | Antimicrobial method | Antimicrobial Concentration | Light/Ultrasonic Paramet | Reference | ESSONS 432-8. |
|---|---------------------------|-------------------|--|---------------------|----------------------------------|-----------------------------|--------------------------|-----------|---------------|
| 1 | THC ME | 5% | HIV-1 | Cell infection | IC ₅₀ | 0.9357 µM | - | [113] | as 2005 |
| | CUR-NE | N/R | HPV | - | aPDT | 80 µM | 50 J/cm ² | [114] | |
| 1 | CUR-NE | N/R | DENV-1 to 4 | Cell infection | Cell viability | 1, 5, 10 µg/mL | - | [115] | and |
| | P60-CUR | 4 mg/L | <i>E. coli</i> | Planktonic | OD595 nm | N/R | - | [116] | |
| 1 | PE:CUR | 0.566 mg/mL | <i>S. aureus</i> , <i>S. epidermidis</i> , <i>S. faecalis</i> , <i>C. albicans</i> , <i>E. coli</i> | Planktonic | Inhibition zone | 1 mg/mL* | - | [117] | Agent. |
| 1 | cu-SEDDS | 1% | <i>E. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>K. pneumonia</i> | Planktonic | MIC | 45–62 µg/mL | - | [118] | g T.2019. |
| 1 | CUR:NE in microbeads | 0.5 mg/mL | <i>E. coli</i> , <i>S. typhimurium</i> , <i>Y. enterocolitica</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>B. cereus</i> , <i>L. monocytogenes</i> | Planktonic | Inhibition zone | 90 and 180 mg/mL* | - | [119] | design |
| 1 | Lignin sulfomethylated | 0.3 mg/mL | <i>S. aureus</i> | Planktonic | OD600 nm | 2.4 mg/mL* | - | [120] | jy |
| 1 | C14-EDA/GM/WC14-MEDA/GM/W | N/R | <i>C. albicans</i> | Planktonic, biofilm | Microdilution assay, antibiofilm | 100 µg/mL, 20 µg | - | [121] | jik; of |

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18. Simin Sharifi; Nazanin Fathi; Mohammad Yousef Memar; Seyed Mahdi Hosseiniyan Khatibi; Rovshan Khalilov; Ramin Negahdari; Sepideh Zununi Vahed; Solmaz Maleki Dizaj; Anti-microbial activity of curcumin nanoformulations: New trends and future perspectives. *Phytotherapy Research* **2020**, *34*, 1926–1946; 10.1002/ptr.6658. Ed. *: formulation concentration.

19. Yaning Gao; WanBo Tai; Ning Wang; Xiang Li; Shibo Jiang; Asim K. Debnath; Lanying Du; Shizhong Chen; Gao; Tai; et al. WangLiDuChen Identification of Novel Natural Products as Effective and Broad-Spectrum Anti-Zika Virus Inhibitors. *Viruses* **2019**, *11*, 1219; 10.3390/v11111019. Cyclic Dextrins (CDs) have revolutionized the pharmaceutical industry in recent years. CDs consist of three naturally occurring oligosaccharides in a cyclic structure produced from starch [123][124][125]. The natural CDs have their nomenclature system and their chemical structure based on the number of glucose residues in their structure:

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Figure 5. Schematic representation of CUR in CD.

23. Chih-Chun Wen; Yuen-Hsiung Kuo; Jia-Tsrong Jan; Po-Huang Liang; Sheng-Yang Wang; Hong-Gi Liu; Ching-Kuo Lee; Shang-Tzen Chang; Chih-Jung Kuo; Shoei-Sheng Lee; et al. Chia-Chung HouPei-Wen HsiaoShih-Chang ChienLie-Fen ShyurNing-Sun Yang Specific Plant Terpenoids and Lignoids Possess Potent Antiviral Activities against Severe Acute Respiratory Syndrome Coronavirus. *Journal of Medicinal Chemistry* 2007, **50**, 4087–4095, [10.1021/jm070295s](https://doi.org/10.1021/jm070295s).

| Type of CD | [CUR] Formulation | Microorganism | Type of Culture | Antimicrobial Method | Antimicrobial [CUR] | Light/Ultrasonic Parameters | Reference |
|---|-------------------------|-------------------------------------|-----------------|---------------------------|---|------------------------------|-----------|
| PEG-based β -CD or γ -CD | 10 μ M | <i>E. coli</i> , <i>E. faecalis</i> | Planktonic | aPDT | 10 μ M | 4.8, 29 J/cm ² | [130] |
| HPMC-stabilized hydroxypropyl- β -CD | 7.64×10^{-3} M | <i>E. coli</i> | Planktonic | aPDT | 10, 25 μ M | 5, 14, 28 J/cm ² | [131] |
| methyl- β -CD hyaluronic acid HPMC | 7.64×10^{-3} M | <i>E. faecalis</i> , <i>E. coli</i> | Planktonic | aPDT | 0.5–25 μ M | 11, 16, 32 J/cm ² | [132] |
| carboxymethyl- β -CD | 20 μ M | <i>E. coli</i> | Planktonic | aPDT | 0.7 ± 0.1 to 4.1 ± 1.6 nmole cm^{-2} | 1050 ± 250 lx | [133] |
| hydrogel with CUR in hydroxypropyl- β -CD | 15.8 mg/mL | <i>S. aureus</i> | Planktonic | Inhibition zone | 2% (w/v) | - | [134] |
| α - and β -CD | 1 mol/L | <i>E. coli</i> , <i>S. aureus</i> | Planktonic | MIC, OD ₆₀₀ nm | 0.25 and 0.31 mg/mL | - | [135] |

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| | | | | | | | | | |
|---|--------------------|---------|--|------------|-------------------------|-----------------|----------------------|-------|-------------------------|
| 3 | β-CD or γ-CD in CS | 0.06 mM | <i>E. coli</i> , <i>S. aureus</i> | Planktonic | MIC, Zone of inhibition | 64 and 32 µg/mL | - | [136] | 60. film ed 21, ends in |
| 3 | γ-CD | 25 mg/L | <i>T. rubrum</i> | Planktonic | MIC, aPDT | N/R | 45 J/cm ² | [137] | |
| 3 | hydroxypropyl-β-CD | 1:1 | <i>B. subtilis</i> , <i>S. aureus</i> , <i>S. pyrogenes</i> , <i>P. aeruginosa</i> , <i>C. difficile</i> , <i>C. butyricum</i> , <i>L. monocytogenes</i> , <i>E. faecalis</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. mirabilis</i> , <i>S. typhimurium</i> , <i>E. aerogenes</i> , <i>C. kusei</i> , <i>C. albicans</i> | Planktonic | Inhibition zone | 25 mg/mL | - | [138] | |
| 3 | methyl-β-CD | 20 mM | <i>E. coli</i> | Planktonic | MIC, MBC, aPDT | 500, 90 µM | 9 J/cm ² | [139] | cial |

BIOTECHNOLOGY 2021, 14, 102-107, 10.1111/1751-7313.13734.

33. Thaila Quatrini Corrêa; Kate Cristina Blanco; Érica Boer Garcia; Shirly Marleny Lara Perez; Daniel José Chianfrone; Vinicius Sigari Morais; Vanderlei Salvador Bagnato; Effects of ultraviolet light and curcumin-mediated photodynamic inactivation on microbiological food safety: A study in meat and fruit. *Photodiagnosis and Photodynamic Therapy* 2020, 30, 101678, 10.1016/j.pdpdt.2020.101678. Concentration. -: not performed. N/R: not reported.

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| Type of CS | [CUR] Formulation | Microorganism | Type of Culture | Antimicrobial Method | Antimicrobial [CUR] | Reference | S- |
|------------|-------------------|----------------------------|--------------------------|---------------------------|---------------------|-----------|-----------------|
| PEG-CS | 4.4%, 5 mg/mL | MRSA, <i>P. aeruginosa</i> | Planktonic, Animal model | OD _{600nm} , CFU | 5 and 10 mg/mL * | [144] | optics80 20043. |

| | | | | | | | |
|---|--------------------------------|--------------------|---|---------------------|---|---------------------------|-------|
| 3 | CCS microspheres | 12.27 mg/mL, 1 mol | <i>S. aureus</i> , <i>E. coli</i> | Planktonic | Zone of inhibition, MIC | N/R | [145] |
| 3 | CS nanoparticles | 1.06 mg/mL | <i>S. mutans</i> | Planktonic, Biofilm | MIC | 0.114 mg/mL | [146] |
| 3 | CS-CMS-MMT | 0.0004–0.004 g | <i>S. mutans</i> | Planktonic, Biofilm | MIC | 0.101 mg/mL | [147] |
| 4 | CS-GP-CUR | 148.09 ± 5.01 µg | <i>S. aureus</i> | Planktonic | Zone of inhibition, tissue bacteria count | N/C | [148] |
| 4 | PVA-CS-CUR | N/C | <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>B. subtilis</i> | Planktonic | Zone of inhibition | N/R | [149] |
| 4 | PVA-CS-CUR | 10, 20, 30 mg | <i>P. multocida</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>B. subtilis</i> | Planktonic | Zone of inhibition | 10, 20, 30 mg | [150] |
| 4 | CS NPs | 2, 4, 8, 16% | <i>C. albicans</i> , <i>S. aureus</i> | Planktonic, Biofilm | MIC, Colony count | 400 mg/mL | [151] |
| 4 | CS NPs | 4 mg/mL | HCV-4 | N/R | Antiviral assay | 15 µg/mL | [152] |
| 4 | CS/milk protein nanocomposites | 100 mg | PVY | Plant infection | Antiviral activity | 500, 1000, 1500 mg/100 mL | [153] |

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extensively drug-resistant (XDR) bacteria isolated from burn wound infections.. *Avicenna J*

Antimicrobial Studies with CUR loaded in other polymeric DDSs are summarized in Table 7.

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| Type of Polymeric DDS | [CUR] Formulation | Microorganism | Type of Culture | Antimicrobial Method | Antimicrobial [CUR] | Light/Ultrasonic Parameters | Reference |
|----------------------------|-------------------|-------------------------------------|-----------------|----------------------|---------------------|--|-----------|
| PEG 400y-CD and PEG + β-CD | 0.18% | <i>E. faecalis</i> , <i>E. coli</i> | Planktonic | CFU/mL aPDT | N/R | 9.7 J/cm ² 29 J/cm ² | [154] |

Biology and Medicine **2019**, *143*, 140-145, 10.1016/j.freeradbiomed.2019.08.003.

| | | | | | | | | |
|---|-----------------------------------|-----------|---|-------------------------------------|------------------------|-------------------|----------------------------------|-------|
| 4 | CUR-NP without polymer | 100 mg | <i>S. aureus</i> , <i>B. subtilis</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>P. notatum</i> , <i>A. niger</i> | Planktonic | MIC Inhibition zone | 100 mg, 0.27 mmol | - | [155] |
| | CUR-NP without polymer | 100 mg | <i>M. lutues</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> | Planktonic | MBC | N/R | - | [156] |
| | Mixed polymer NP | 5 mM | <i>E. coli</i> | Planktonic | MIC | 400–500 μ M | - | [157] |
| 4 | CTABTween 20Sodium dodecylsulfate | 100 mg/mL | <i>L. monocytogenes</i> | Planktonic | Inhibition zone | N/R | - | [158] |
| | PLA/dextran sulfate | 4 mg/mL | MRSA, <i>C. albicans</i> , <i>S. mutans</i> | Planktonic/mono- and –mixed biofilm | aPDT | 260 μ M | 43.2 J/cm ² | [159] |
| | PLA/dextran sulfate | 0.4% | <i>C. albicans</i> | Animal model | aPDT | 260 μ M | 37.5 J/cm ² | [160] |
| 5 | Nanocurcumin | N/R | <i>P. aeruginosa</i> (isolates) and standard strain | Planktonic | MIC | 128 μ g/mL | - | [161] |
| | PLGA | 5 mg | <i>S. saprophyticus</i> subsp. <i>Bovis</i> , <i>E. coli</i> | Planktonic | aPDT | 50 μ g/mL | 13.2 J/cm ² | [162] |
| | Eudragit L-100 | N/C | <i>L. monocytogenes</i> | Planktonic | Animal model infection | N/R | - | [163] |
| 5 | nCUR | N/R | <i>S. mutans</i> | PlanktonicBiofilm | Inhibition zoneaPDT | N/R | 300–420 J/cm ² | [164] |
| | nCUR combined with indocyanine | 100 mg | <i>E. faecalis</i> | Biofilm | Metabolic activity | N/R | 500 mW/cm ² | [165] |
| | PVAc-CUR-PET-PVDC | 0.02 g | <i>S. aureus</i> , <i>S. tephimurium</i> | Planktonic | aPDT | N/R | 24, 48, and 72 J/cm ² | [166] |
| 5 | MOA.CUR-PLGA-NP | Up to 10% | <i>S. mutans</i> | Biofilm | aPDT | 7% wt | 45 J/cm ² | [167] |
| | CS- β -CD | N/C | <i>S. aureus</i> , <i>E. coli</i> | Planktonic | Colony count | Up to 0.03% | - | [168] |

53. Sivadas Ganapathy; Shan Sainudeen; Veena S Nair; Mohammad Zarbah; Anshad Mohamed Abdulla; Chawre Mustafa Najeeb; Can herbal extracts serve as antibacterial root canal irrigating solutions? Antimicrobial efficacy of *Tylophora indica*, *Curcumin longa*, *Phyllanthus amarus*, and sodium hypochlorite on *Enterococcus faecalis* biofilms formed on tooth substrate: In vitro study. *Journal of Pharmacy And Bioallied Sciences* **2019**, 12, 423-S429, 10.4103/jpbs.jpbs_127_20.

54. Arash Azizi; Parastoo Shohrati; Mehdi Goudarzi; Shirin Lawaf; Arash Rahimi; Comparison of the effect of photodynamic therapy with curcumin and methylene Blue on *streptococcus mutans* bacterial colonies. *Photodiagnosis and Photodynamic Therapy* **2019**, 27, 203-209, 10.1016/j.pdpd.2019.06.002.

56. Jeniffer Machado Soane; Fernanda Oliveira Reis; Silvana Mayumi Inada; Vanderlei Salvador Bagnato; Kate Cristina Blanco; Optimization for microbial incorporation and efficiency of

3.8. CUR with Metallic Nanoparticles

photodynamic therapy using variation on curcumin formulation. *Photodiagnosis and Photodynamic Therapy* **2020**, *29*, 101652, [10.1016/j.pdpdt.2020.101652](https://doi.org/10.1016/j.pdpdt.2020.101652).

Metal complexation plays an important role in the therapeutic properties of CUR. The β -diketone moiety in the CUR

56. Daniela Alejandra Ousicanqui Méndez; Eliezer Gutierrez; Giuliana Campos Chaves Lamarque; the

chemical structure enables it to form complexes with metals. In a previous review summarized;

antimicrobial activity of CUR and its complexes with metals, such as boronate, Al^{3+} , Fe^{2+} , Cu^{2+} ,

Fe Machado, Thiago Greinert; The effectiveness of curcumin-mediated antimicrobial photodynamic

therapy depends on pre-irradiation and biofilm growth times. *Photodiagnosis and Photodynamic*

Therapy **2019**, *27*, 474-480, [10.1016/j.pdpdt.2019.07.011](https://doi.org/10.1016/j.pdpdt.2019.07.011) this context, silver NPs (AgNPs) have been

57. Xinlong Li; Luoping Yih; Gordon Ramage; Bingchun Li; Ye Tao; Qinghui Zhi; Huancai Lin; Yan

metals are summarized in Table 8.

Zhou; Assessing the impact of curcumin on dual-species biofilms formed by *Streptococcus*

mutans and *Candida albicans*. *MicrobiologyOpen* **2019**, *8*, e937, [10.1002/mbo3.937](https://doi.org/10.1002/mbo3.937).

58. Marzieh Mahdizadeh-Ari; Maryam Pourhajibagher; Abbas Bahador; Changes of microbial cell survival, metabolic activity, efflux capacity, and quorum sensing ability of *Aggregatibacter actinomycetemcomitans* due to antimicrobial photodynamic therapy-induced bystander effects. *Photodiagnosis and Photodynamic Therapy* **2019**, *26*, 287-294, [10.1016/j.pdpdt.2019.04.021](https://doi.org/10.1016/j.pdpdt.2019.04.021).

59. Hui Pan; Dongqing Wang; Fengqiu Zhang; In vitro antimicrobial effect of curcumin-based photodynamic therapy on *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*. *Photodiagnosis and Photodynamic Therapy* **2020**, *32*, 102055, [10.1016/j.pdpdt.2020.102055](https://doi.org/10.1016/j.pdpdt.2020.102055).

60. Sarah Böcher; Johannes-Simon Wenzler; Wolfgang Falk; Andreas Braun; Comparison of different laser-based photochemical systems for periodontal treatment. *Photodiagnosis and Photodynamic Therapy* **2019**, *27*, 433-439, [10.1016/j.pdpdt.2019.06.009](https://doi.org/10.1016/j.pdpdt.2019.06.009).

61. Lucas Henrique De Paula Zago; Sarah Raquel de Annunzio; Kleber Thiago de Oliveira; Paula Aboud Barbugli; Belen Rétamal Valdés; Magda Feres; Carla Raquel Fontaná; Antimicrobial photodynamic therapy against metronidazole-resistant dental plaque bacteria. *Journal of Photochemistry and Photobiology B: Biology* **2020**, *209*, 111903, [10.1016/j.jphotobiol.2020.111903](https://doi.org/10.1016/j.jphotobiol.2020.111903)

Figure 6. Schematic representation of CUR in silver nanoparticles.

Table 8. Antimicrobial studies performed with CUR complexes with metallic NPs.

| Type of Metallic Material | [CUR] Formulation | Microorganism | Type of Culture | Antimicrobial Method | Antimicrobial [CUR] | Reference |
|---------------------------|-------------------|--|-----------------|----------------------|---------------------|-----------|
| CUR-AgNPs | 20 mg/mL | <i>P. aeruginosa</i> , <i>E. coli</i> , <i>B. subtilis</i> , <i>S. aureus</i> | Planktonic | MIC | 20 mg/mL | [173] |
| Ag-CUR-nanoconjugates | 0.1 mM | <i>E. coli</i> , <i>Salmonella</i> | Planktonic | Zone of Inhibition | 0.1 mM | [174] |

planning in the treatment of residual pockets in diabetic patients: A randomized and controlled split-

| | | | | | | | |
|---|-----------------------------------|------------|---|------------|-----------------------------|--------------------------------|---------|
| | | | spp., <i>Fusarium</i> spp., <i>S. aureus</i> | | | | 6/j.pdp |
| 6 | AgCURNPs | 500 mg | <i>P. aeruginosa</i> <i>S. aureus</i> | Biofilm | CLSM SEM | Up to 400 μ g/mL | [175] |
| | AgNPs | 7 mg | <i>E. coli</i> | Planktonic | Turbidimetric Assay | 0.005 μ M | [176] |
| 6 | cAgNPs | 7 mg | <i>E. coli</i> <i>B. subtilis</i> | Planktonic | MIC, CFU/mL | 7 mg | [177] |
| 6 | Ru II complex | 0.092 g | <i>E. coli</i> , <i>S. aureus</i> , <i>K. pneumoniae</i> , <i>A. baumannii</i> , <i>P. aeruginosa</i> , <i>Enterococcus</i> sp. | Planktonic | MIC/FICI | >64 μ g/mL | [178] |
| 6 | SCMC SNCF nanocomposites with CUR | 0.25 mg/mL | <i>E. coli</i> | Planktonic | Disc Method Count Method | 2 mg/mL | [179] |
| 6 | CSCL CUR-AgNP | 0.092 g | <i>E. coli</i> , <i>B. subtilis</i> | Planktonic | Zone of Inhibition | 10 and 20 μ M | [180] |
| | nSnH | 10% | <i>S. aureus</i> , <i>E. coli</i> | Planktonic | CFU/mL | N/R | [181] |
| 6 | Nanocomposite of CUR and ZnO NPs | N/C | <i>S. epidermidis</i> , <i>S. hemolyticus</i> , <i>S. saprophyticus</i> | Planktonic | Zone of Inhibition | 1000, 750, 500, 250 μ g/mL | [182] |
| 6 | Thermo-responsive hydrogels | N/C | <i>S. aureus</i> <i>P. aeruginosa</i> <i>E. coli</i> | Planktonic | MIC | 400 μ g/mL | [183] |
| 6 | CUR-AgNPs | 5 mg/mL | <i>C. albicans</i> , <i>C. glabrata</i> , <i>C. tropicalis</i> , <i>C. parapsilosis</i> , <i>C. krusei</i> , <i>C. kefyr</i> | Planktonic | Zone of Inhibition, MIC | 32.2–250 μ g/mL | [184] |
| 7 | Gel-CUR-Ag | 20 mg | <i>P. aeruginosa</i> , <i>S. aureus</i> | Planktonic | MIC, MBC | 20 mg | [185] |
| | HGZ-CUR | N/C | <i>S. aureus</i> , <i>T. rubrum</i> | Planktonic | Zone of Inhibition | N/C | [186] |
| 7 | CHG-ZnO-CUR | N/C | <i>S. aureus</i> , <i>T. rubrum</i> | Planktonic | Zone of Inhibition | N/C | [187] |

Goldman; Ewerton Garcia De Oliveira Mima; Verapamil inhibits efflux pumps in *Candida albicans*, exhibits synergism with fluconazole, and increases survival of *Galleria mellonella*. *Virulence* **2020**, *12*, 231–243, 10.1080/21505594.2020.1868814.

| | | | | | | | | |
|---|------------------------------|-------------------------|---|--------------------------------|---------------------------|--------------------------|-------|----------------|
| 7 | Copper (II) oxide NPs | 1 g | <i>E. faecalis</i> , <i>P. aeruginosa</i> | Planktonic | Zone of Inhibition CFU/mL | 1 mg/mL | [188] | Ikashony and |
| 7 | OA-Ag-C | 1 g | <i>P. aeruginosa</i> , <i>S. aureus</i> | Planktonic | OD _{600nm} | 2.5 mg/mL | [189] | 4. |
| 7 | Ag-NP- β -CD-BC | 0.79 g | <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>C. auris</i> | Planktonic | Zone of Inhibition | N/R | [190] | 0.3390/ |
| 7 | Cotton fabrics coated ZnO-NP | 2.71×10^{-3} M | <i>S. aureus</i> , <i>E. coli</i> | Planktonic | Bacterial Count | N/R | [191] | 7, 40, ends as |
| 7 | CS-ZnO-CUR | 0.2 g | <i>S. aureus</i> , <i>E. coli</i> | Planktonic | MIC, MBC | Up to 50 μ g/mL | [192] | |
| 7 | CUR-TiO ₂ -CS | 100–300 mg | <i>S. aureus</i> , <i>E. coli</i> | Planktonic Animal infection | MIC | 10 mg | [193] | ACE2 n. |
| 7 | CUR-Au-NPs | 1 mg/mL | <i>E. coli</i> , <i>B. subtilis</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> | Planktonic | Zone of Inhibition | 100, 200, 300 μ g/mL | [194] | |

7. MUNIL KUMAR, KUSHNEET KAUR SAINI, DILEEP KUMAR SINGH, Addressing the potential role of curcumin in the prevention of COVID-19 by targeting the Nsp9 replicase protein through molecular docking. *Archives of Microbiology* **2021**, *203*, 1691–1696, 10.1007/s00203-020-02163-[CUR]: CUR concentration. N/R: not reported. N/C: not clear.

7.9. **CUR in Mesoporous Particles**
 Karyala; Virtual screening of curcumin and its analogs against the spike surface glycoprotein of SARS-CoV-2 and SARS-CoV. *Journal of Biomolecular Structure and Dynamics* **2021**, *5*, 19, 1–10. <https://doi.org/10.1080/07391102.2020.1868328> Porous (from 2 up to 50 nm), and macroporous (above 50 nm) [195]. Porous materials can be synthesized using carbon, silica, and metal oxides [196]. Mesoporous silica nanoparticles (MSN, 79. Loubna Allam; Fatima Ghribi; Hakmi Mohammed; Naima El Hafidi; Rachid El Jaoudi; Jaouad El Figure 7) are inorganic scaffolds [197] which seemed ideal carriers for hydrophobic drugs due to their well-defined Harti; Badreddine Lmimouni; Lahcen Belyamani; Azeddine Ibrahimi; Targeting the GRP78- structure, large specific surface area, and versatile chemistry for functionalization [198]. The pore size and volume Dependant SARS-CoV-2 Cell Entry by Peptides and Small Molecules. *Bioinformatics and Biology Insights* **2019**, *14*, 117793220965505, 10.1177/117793220965505. and the surface area, as well as the surface functionalization of the mesoporous material, determine the drug load and release [199]. Moreover, mesoporous materials can be modified or functionalized to control drug release under 80. Mahmoud A.A. Ibrahim; Alaa H.M. Abdelrahman; Taha A. Hussien; Esraa A.A. Badr; Tarek A. environmental stimuli, such as pH, temperature, or light. These stimuli responsive DDS, or smart DDS, prevent Mohamed; Hesham R. El Seedi; Paul W. Pare; Thomas Efferth; Mohamed Elmir F. Hegazy; In undesirable drug release before reaching the target tissue (zero premature release) [199]. Antimicrobial studies with CUR in porous DDS are summarized in Table 9.

Computers in Biology and Medicine **2020**, *126*, 104046-104046, 10.1016/j.combiomed.2020.104 046.

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Pore

83. Jiao Wang; Xiaoli Zhang; Alejandra B. Omarini; Binglin Li; Virtual screening for functional foods, **Figure 7.** Schematic representation of a porous particle. against the main protease of SARS-CoV-2. *Journal of Food Biochemistry* **2020**, *44*, 13481, 10.1111/jfbc.13481.

84. Debmalya Barh; Sandeep Tiwari; Marianna E. Weener; Vasco Azevedo; Aristóteles Góes-Neto; M. Michael Gromiha; **Porous Particle**; Multi-omics-based identification of SARS-CoV-2 infection biology and candidate drugs against COVID-19. *Computers in Biology and Medicine* **2020**, *126*, 104051-104051, 10.1016/j.compbiomed.2020.104051.

Table 9. Antimicrobial studies performed with CUR in porous DDSs.

85. Dantong Zheng; Chongxing Huang; Haohe Huang; Yuan Zhao; Muhammad Rafi Ullah Khan; Hui

| Porous DDS | [CUR] Formulation | Microorganism | Type of Culture | Antimicrobial Method | Antimicrobial [CUR] | Light/Ultrasonic Parameters | Reference |
|----------------------------------|-----------------------|-----------------------------------|-------------------|-----------------------------|---------------------|-----------------------------|-----------|
| Cu-SNP/Ag | 1.0 mmol | <i>E. coli</i> | Planktonic | aPDT | N/R | 72 J/cm ² | [200] |
| Bionanocomposite silica/chitosan | 100 mg | <i>E. coli</i> , <i>S. aureus</i> | Planktonic | Zone of inhibition | N/R | - | [201] |
| NCIP | 1 mg | HIV-1 | Transfected cells | Immuno fluorescent staining | 5–8 mg/mL | - | [202] |
| Lollipop-like MSN | 30 mg L ⁻¹ | <i>E. coli</i> , <i>S. aureus</i> | Planktonic | OD _{600nm} | N/R | - | [203] |
| SBA-15/PDA/Ag | 2 mg | <i>E. coli</i> , <i>S. aureus</i> | Planktonic | CFU/mL | 50 mM | - | [204] |

8 John Francis Callan; Antimicrobial sonodynamic and photodynamic therapies against *Candida albicans*. *Biofouling* **2018**, *34*, 357-367, 10.1080/08927014.2018.1439935.

89. Fatemeh Forouzanfar; Ali Forouzanfar; Thozhukat Sathyapalan; Hossein M. Orafai; Amirhossein Sahebkar; Curcumin for the Management of Periodontal Diseases: A Review. *Current Pharmaceutical Design* **2020**, *26*, 4277-4284, 10.2174/138161282666200513112607.

3.10. CUR in Quantum Dots

90. Kourosh Cheraghipour; Behrouz Ezatpour; Leila Masoori; Abdolrazagh Marzban; Asghar

Sepahvand; Arian Karimi Rouzbahani; Abbas Moridnia; Sayyad Khanizadeh; Hossein Mahmoudvand; Anti-*Candida* Activity of Curcumin: A Systematic Review. *Current Drug Discovery Technologies* **2021**, *18*, 379-390, 10.2174/1570163817666200518074629. Quantum dots (QDs) are semiconductor particles at nanosize (up to 10 nm) with electrical and photoluminescence properties of biotechnological and biomedical applications, such as bioimaging and DDS [205]. Carbon dots are divided into carbon QD and graphene QD and are produced by top-down and bottom-up methods using bulk synthesis, *in situ* synthesis, *green* synthesis, and *bottom-up* synthesis. Carbon dots have a high surface area and are used as drug delivery systems. *Advanced Drug Delivery Reviews* **2001**, *47*, 113-131, 10.1016/s0169-409x(00)00124-1.

91. Kurozumi Kitaoka; Atsushi Harada; Yukio Nagasawa; **205**; Antimicrobial mixed micelles for CUR delivery are synthesized, characterized and evaluated for CUR delivery. *Advanced Drug Delivery Reviews* **2001**, *47*, 113-131, 10.1016/s0169-409x(00)00124-1.

Table 10. Antimicrobial studies performed with CUR in quantum dots (QDs).

92. Muhammad Usman Akbar; Khalid Mahmood Zia; Ahsan Nazir; Jamshed Iqbal; Syeda Abida Ejaz; Muhammad Sajid Hamid Akash; Pluronic-Based Mixed Polymeric Micelles Enhance the

| Type of Material | [CUR] Formulation | Microorganism | Type of Culture | Antimicrobial Method | Antimicrobial [CUR] | Light/Ultrasonic Parameters | Reference | 2249-0 |
|------------------|-------------------|---|------------------------------------|--|----------------------|-----------------------------|-----------|------------------------|
| C | CUR-cQDs | 0.6 <i>S. aureus</i> MRSA <i>E. faecalis</i> <i>E. coli</i> <i>K. pneumoniae</i> <i>P. aeruginosa</i> | Planktonic Biofilm | Grown inhibition Biomass evaluation Confocal microscopy | 3.91–7.825 µg/mL | - | [206] | inqui ced csami. |
| G | CUR-cQDs | 200 mg EV-71 | Cell infection Animal infection | MIC Plaque assay TC IC50 assay Western blot PCR | 5 µg/mL | - | [207] | n s11033 |
| G | CUR-MQD | 2:1 wt% <i>K. pneumoniae</i> <i>P. aeruginosa</i> <i>S. aureus</i> | Planktonic | MIC MBC Confocal microscopy Fluorescence microscopy Flow cytometry | <0.00625–0.125 µg/mL | - | [208] | ct in .2017. |
| G | CUR-GQDs | N/C A. actinomycetemcomitans <i>P. gingivalis</i> <i>P. intermedia</i> | Mixed biofilm | aPDT | 100 µg/mL | 60–80 J/cm ² | [209] | Email us |

nanomicelle curcumin. *Photodiagnosis and Photodynamic Therapy* **2020**, *30*, 101780, 10.1016/j.pdpt.2020.101780.

97. Katia Rupel; Luisa Zupin; Silvia Brich; Mario Mardirossian; Giulia Ottaviani; Margherita Gobbo; Roberto Di Lenarda; Sabrina Pricl; Sergio Crovella; Serena Zacchigna; et al. Matteo Biasotto. Antimicrobial activity of amphiphilic nanomicelles loaded with curcumin against *Pseudomonas aeruginosa* alone and activated by blue laser light. *Journal of Biophotonics* **2020**, *14*, null, 10.1002/jbio.202000350.

98. Victor Hugo Cortez Dias; Amanda Milene Malacrida; Adrielle Rodrigues dos Santos; Andreia Farias Pereira Batista; Paula Aline Zanetti Campanerut-Sá; Gustavo Braga; Evandro Bona; Wilker Caetano; Jane Martha Graton Mikcha; pH interferes in photoinhibitory activity of curcumin nanoencapsulated with pluronic® P123 against *Staphylococcus aureus*. *Photodiagnosis and Photodynamic Therapy* **2021**, *33*, 102085, 10.1016/j.pdpt.2020.102085.

99. Yanhui Zhu; Qiaojie Luo; Hongjie Zhang; Qiuquan Cai; Xiaodong Li; Zhiqian Shen; Weipu Zhu; A shear-thinning electrostatic hydrogel with antibacterial activity by nanoengineering of polyelectrolytes. *Biomaterials Science* **2019**, *8*, 1394-1404, 10.1039/c9bm01386e.

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102. Soumitra Shome; Anupam Das Talukdar; Manabendra Dutta Choudhury; Mrinal Kanti Bhattacharya; Hrishikesh Upadhyaya; Curcumin as potential therapeutic natural product: a nanobiotechnological perspective. *Journal of Pharmacy and Pharmacology* **2016**, *68*, 1481-1500, 10.1111/jphp.12611.

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