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).

Keywords: 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/U Parame
DMSO (0.4%)	ZIKV >DGEV	Cell infection	IC_{50} $>IC_{90}$	5.62–16.57 μM	
N/R	HPVA Tulane V	Cell infection	Viral survival	0.015 mg/mL	
N/R	KSPV	Infected cells	EC_{50}	Up to 6.68 μM	
Aqueous *Piper nigrum* seed extract	SARS-CoV-2	Cell infection	IC_{50} Plaque reduction	0.4 μg/mL	
DMSO (<0.4%)	SARS-CoV-1	Cell infection	Inhibiton of viral replication	20 μM	
N/R	SARS-CoV	In vitro	Viral inhibition	23.5 μM	
N/R	SARS-CoV	In vitro	papain-like inhibition	5.7 μM	
DMSO (1 *w*/*v*)	*S. aureus* *E. coli*	Planktonic	Inhibition zone MIC	600 and 400 μg/mL	
DMSO	MRSA	Planktonic	MIC FICI	15.5 μg/mL	
N/R	*S. aureus* MSSA MRSA	Planktonic	Colony count	100 μg/mL	8 o
DMSO (10%)	*S. aureus*	Biofilm	aPDT	20, 40, and 80 μM	5.
DMSO	VRSA	Biofilm/animal infection model	MIC MBC	156.25 μg/mL	2
N/R	*S. aureus*	Animal infection model	aPDT	78 μg/mL	6
DMSO	*S. aureus*	Infected fruit	Survival fraction	100 nM	1.5 a
N/R	*S. aureus* *E. coli*	Planktonic	PDI	40 and 80 μM	1
Tween 80 (0.5%)	*S. aureus*	Planktonic	CFU/mL	300 and 500 μM	0.03-
N/R	*S. aureus*	Biofilm	Confocal microscope	N/R	170
DMSO (0.5%)	*S. aureus*	Biofilm	SDT aPDT SPDT	80 μM	15 a 100 H
DMSO	*E. coli*	Planktonic	MIC Inhibition zone	110, 220 and 330 μg/mL	
DMSO	*E. coli*	Planktonic	OD_{600nm}	8,16, 32, and 64 μg/mL	
N/R	*S. dysenteriae* *C. jejuni*	Planktonic	MIC/MBC	256 and 512 μg/mL	
Edible alcohol	*E. coli*	Planktonic	aPDT	5, 10, and 20 μM	3
DMSO	*H. pylori*	Planktonic biofilm	MIC MBC aPDT	50 μg/mL	10
DMSO	*P. aeruginosa*	Biofilm	aPDT CFU/mL	N/R	5 an
DMSO	Imipenem-resistant *A. baumannii*	Planktonic	aPDT	25, 50, 100, and 200 μM	5

Solvent	Microorganism	Culture	Antimicrobial Method	CUR Concentration	Light/U Parame
DMSO (2%)	*P. aeruginosa, A. baumannii, K. pneumoniae, E. coli, E. faecalis*	Planktonic	MIC/FICI	128-256 µg/mL	
N/R	*C. difficile, C. sticklandii, B. fragilis, P. bryantii*	Planktonic	Viable cell number	10 µg/mL	
N/R	*B. subtillis, E. coli, S. carnosus, M. smegmatis*	Planktonic	MIC/MBC	Up to 25 µM	
N/R	MRSA MSSA *E. coli*	Planktonic/animal infection model	MIC	4–16 µg/mL 2–8 µg/mL 8–32 µg/mL	
N/R	*E. faecalis, S. aureus, B. subtillis, P. aeruginosa, E. coli*	Planktonic	MIC	156 µg/mL	
DMSO (0.5%)	*A. hydrophila, E. coli E. faecalis, K. pneumoniae, P. aeruginosa, S. aureus, C. albicans*	Planktonic	MIC/MBC/ FICI/aPDT	37.5–150 µg/mL	
N/R	*E. faecalis*	Infection model	CFU/mL	1 µg/mL	
Commercial solution	*E. faecalis*	Biofilm	aPDT	1.5 g/mL	2(
Ethanol 99%	*A. hydrophila, V. parahaemolyticus*	Planktonic	aPDT/SDT	Up to 15 mg/L	
DMSO (10%)	*E. faecalis*	Biofilm	MIC/MBC	120 mg/mL	
N/R	*S. mutans*	Planktonic	aPDT	10 g/100cc	
DMSO: ethyl alcohol	*S. mutans, S. pyogenes*	Planktonic	aPDT	3 mg/mL	28
DMSO (0.8%)	Caries isolated	Biofilm	aPDT	600 µg/mL	7
DMSO	*S. mutans, C. albicans*	Biofilm single/dual	MBEC	0.5 mM	
DMSO (0.05 M)	*A. actinomycetemcomitans*	Planktonic	aPDT	40 µg/mL	300
DMSO (<1%)	*P. gingivalis, A. actinomycetemcomitans*	Planktonic	aPDT	20 µg/mL	6, 12
DMSO (0.5%)	*P. gingivalis, A. actinomycetemcomitans, C. rectus, E. corrodens, F. nucleatum, P. intermedia, P. micra, T. denticola, T. forsythis*	Biofilm	aPDT	100 mg/L	
N/R	Subgingival plaque	Biofilm	aPDT	100 µg/mL	3
DMSO	*P. gingivalis*	Planktonic	MIC	12.5 µg/mL	
Ethanol: DMSO (99.9%: 0.1%)	Periodontal pocket	-	aPDT	100 mg/mL	7.
Tween 80	*Streptococcus* spp, *Staphylococcus* spp, *Enterobacteriaceae*, *C. albicans*	Clinical trail	aPDT	0.75 mg/mL	2(
Sodium hydroxide: PBS	*C. albicans, C. parapsilosis, C. glabrata, C.dubliniensis*	Planktonic/biofilm	MIC	0.1–0.5 mg/mL	
N/R	*C. albicans, S. aureus*	Planktonic Biofilm	MIC/Biofilm percentag	200 µg/mL	
N/R	*C. albicans*	Biofilm	aPDT	1.5 g/mL	2(
DMSO (10%)	*C. albicans*	Biofilm	aPDT	20, 40, 60 and 80 µM	2.64 10.56, a
DMSO (1%)	*C. albicans*	Biofilm	aPDT	40 and 80 mM	37.5 a
N/R	*C. albicans*	Biofilm	aPDT	100 µM	1

Solvent	Microorganism	Culture	Antimicrobial Method	CUR Concentration	Light/U Parame
DMSO (2.5%)	Fluconazole-resistant *C. albicans*	Planktonic/biofilm/infection model	MIC/ aPDT	40 µM	5.
	Fluconazole-susceptible *C. albicans*			80 µM	4(
DMSO	*C. albicans, F. oxysporum, A. flavus, A. niger, C. neoformans*	Planktonic	MIC	137.5–200 µg/mL	

2.1. Antiviral Activity

The antiviral activity of CUR has been described against enveloped and non-enveloped DNA and RNA viruses, such as HIV, Zika, chikungunya, dengue, influenza, hepatitis, respiratory syncytial viruses, herpesviruses, papillomavirus, arboviruses, and, noroviruses [11][73][74]. The action mechanism of CUR involves the inhibition of viral attachmentand penetration into the host cell and interference with viral replication machinery and the host cell signaling pathways used for viral replication. Moreover, CUR works as a virucidal substance, acting on the viral envelope or proteins [11][73][74]. CUR in 0.4%vol/vol DMSO was able to inhibit several strains of the Zika virus, including those causing human epidemics, inhibiting the viral attachment to the host cell [19]. The inhibitory effect was potentiated when CUR was combined with gossypol, which is another natural product. CUR also inhibited human strains of the dengue virus [19]. The combination of CUR with heat treatment reduced the time and temperature needed for inactivating the foodborne enteric virus (hepatitis A virus and Tulane virus—a cultivable surrogate of the human norovirus) [20]. CUR was able to inhibit the lytic replication of Kaposi's sarcoma-associated herpesvirus (KSHV) as well as reduce its pathogenesis (neoangiogenesis and cell invasionof 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 replication) [75][80], receptor-binding domains (RBD) of the viral spike protein [76,78,82], human cell receptors angiotensin-converting enzyme2 (ACE2) [76][82], and glucose-regulating protein 78 (GRP78) [79], as well as the RBD/ACE complex [76]. Nevertheless, a virtual screening evaluated the interaction between potential functional foods and the main protease of SARS-CoV-2 and found that CUR showed lower docking affinity than flavonoids, vitamin, and β-sitosterol [83]. Omics approaches have been studied to identify infection pathways and propose drugs that could target these pathways. Thus, an integrative multiomics (interactome, proteome, transcriptome, andbibliome) analysis identified biological processes and SARS-CoV-2 infection pathways and proposed CUR as a potential prophylactic agent for blocking the SARS-CoV-2 infection [84].Although most investigations have evaluated the potential of CUR against SARS-CoV-2 by computational simulations, an in vitro study showed that an immunomodulatory herbal extract composed of CUR and piperine presented a virucidal effect (viral inhibitionof up to 92%) on SARS-CoV-2 [22]. Other in vitro studies showed the ability of CUR to inhibit its viral predecessor —the SARS-CoV-1 [23][24]. CUR in DMSO (<0.4%) inhibited by 25–50% the cytopathogenic effect of SARS-CoV-1 on Vero E6 cells and by 50% the viral replication and 3CL protease (main protease) [23]. Another study used CUR as a positive control for 3CL protease inhibition [24]. CUR also inhibited the papain-like protease, which is another protease used for SARS-CoV replication [25].

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 combinationwas synergistic [27]. Moreover, CUR absorbs blue light (400–500 nm) and is used as anatural 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 $\log_{10}$, while CUR alone reduced their survival by 2 $\log_{10}$ [28]. The aPDT mediated by CUR in 10% DMSO reduced the biofilm viability of *S. aureus* and MRSA by 3 and 2 $\log_{10}$, respectively, and their metabolicactivity 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 $\log_{10}$ 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-mediatedaPDT 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 meatand fruit [33]. Compared to another natural PS, aloe-emodin, CUR was less effective inphotokilling *S. aureus* and *E. coli* [34]. Three-dimensional _cages fabricated with CURand resin monomer (pentaerythritol triacrylate) polymerized by infrared light were usedto entrap and kill S. aureus. Irradiation of μcages for 10 min with visible light resulted in a bacteria mortality rate of 95% [35]. Following the principles of aPDT, SonodynamicTherapy (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 [88].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 μg/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 byCUR and light reduced the viability of *E. coli* by 3.5 log, increased membrane permeabilityof bacteria, and decontaminated oysters [40]. CUR-mediated aPDT reduced the viability of *Helicobacter pylori* and its virulence factors (motility, urease production, adhesion toerythrocytes, 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 *Acetoanaerobium* (*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 thegrowth 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 irradiationeradicated planktonic cultures of *Streptococcus mutans*, which is the main etiologic factor of dental caries [54]. A formulation of syrup with curcuminoids and 30% sucrose wasused as a PS in aPDT, which reduced the viability of *S. mutans*, *Streptococcus pyogenes*, and aclinical 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 glucosyltransferaseand 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 cellsexposed 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 reducedthe 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 microorganismsfrom 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 strainand 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 mediatedby CUR and another PS, Photodithazine®, 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 synthetized 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 moleculardocking analysis showed that MACs had binding affinity to sterol 14α-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**.

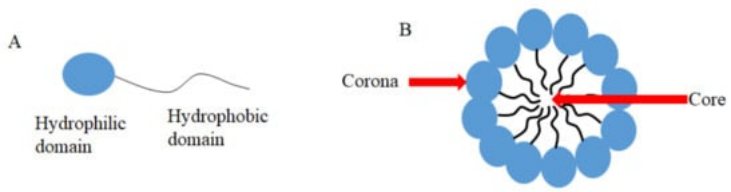

Figure 1. Schematic representation of: (**A**) an amphiphilic molecule and (**B**) an assembled micelle.

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	Refe
Mixed polymer micelles	1000 ppm	*E. coli*, *S. aureus*, *A. niger*	Planktonic	MIC	350 and 275 µg/mL	-	
PCL-*b*-PAsp and Ag	2 mg/mL	*P. aeruginosa*, *S. aureus*	Planktonic	OD_{600nm}	8–500 µg/mL	-	
mPEG-OA	1:10	*P. aeruginosa*	Planktonic	MIC	400 µg/mL	-	
PEG-PCL	10 mg	*C. albicans*	Planktonic	MIC	256 µg/mL	-	
PEG-PE	50 mM	*S. mutans*	Planktonic	SACT	50 mM	1.56 W/cm^2	
DAPMA, SPD, SPM	0.32 mg/mL	*P. aeruginosa*	Planktonic	OD_{600nm} and aPDT	250, 500 nM, 1 µM and 50, 100 nM	18 and 30 J/cm^2	
P123	0.5% *w*/*V*	*S. aureus*	Planktonic	aPDT	7.80 µmol/L	6.5 J/cm^2	
PCL-*b*-PHMG-*b*-PCL, STES	10 mg	*S. aureus*,*E. coli*	Planktonic	MIC	16 and 32 µg/mL *	-	
CUR-PLGA-DEX	1 mg/mL	*P. fluorescens*, *P. putida*	Planktonic biofilm	OD_{600nm} antibiofilm	0.625–5 mg/mL	-	

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.

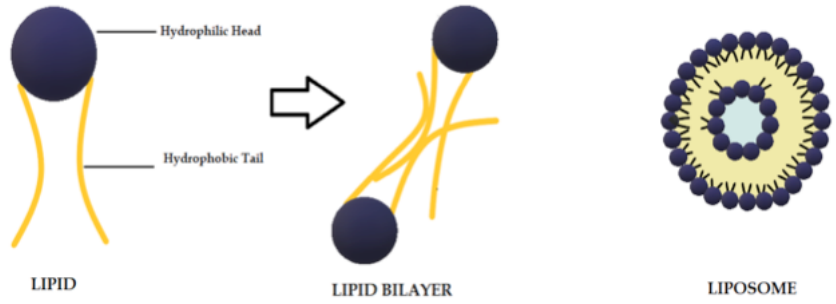

Figure 2. Schematic representation of the liposome structure.

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

Type of Liposomes or SLN	[CUR] Formulation	Microorganism	Type of Culture	Antimicrobial Method	Antimicrobial [CUR]	Reference
Lecithin and cholesterol	0.5 mg/mL	*A. sobria, C. violaceum, A. tumefaciens*	Planktonic biofilm	MIC, antibiofilm	420, 400, and 460 µg/mL	[104]
PCNL	60.65 ± 1.68 µg/µl	*B. subtilis, K. pneumoniae, C. violaceum, E. coli, M. smegmatis, A. niger, C. albicans, F. oxysporum*	Planktonic	Disk diffusion assay	N/R	[105]
Phosphocolines	100:1 M	*S. aureus*	Planktonic	MIC	7 µg/mL	[106]
PLGA: triglycerides: F68	0.8 mg/mL	*E. coli, S. typhimurium, P. aeruginosa, S. aureus, B. sonorensis, B. licheniformis*	Planktonic	MIC	75 and 100 µg/mL	[107]
Soya lecithin and menthol	0.5 mg/mL	MRSA	Planktonic, Biolfim	MIC, microscopy, biomass	10 and 125 µg/mL	[108]

Type of Liposomes or SLN	[CUR] Formulation	Microorganism	Type of Culture	Antimicrobial Method	Antimicrobial [CUR]	Reference
Lecithin and cholesterol	0.5 mg/mL	*A. sobria, C. violaceum, A. tumefaciens*	Planktonic biofilm	MIC, antibiofilm	420, 400, and 460 µg/mL	[104]
CurSLN	60 mg/500 mg lipid	*S. aureus, S. mutans, V. streptococci, L. acidophilus, E. coli, C. albicans*	Planktonic	MIC, MBC	0.09375–3 and 1.5–6 mg/mL	[109]

[CUR]: CUR concentration. N/R: not reported.

3.3. CUR in Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLN, Figure 3, Table 3) are a modern type of lipid-based carrier composed by solid biodegradable lipids and spherical solid lipid particles. SLNs are water colloidal or aqueous surfactant solution systems [102]. SLNs have advantages such as biocompatibility, biodegradability, greater drug absorption, and drug retention [18][102], thus they are an interesting system to carry CUR [14]. Currently, SLNs have become popular because they are used as carriers for COVID-19 vaccines based on RNA vaccine technology (Moderna and Pfizer–BioNTech).

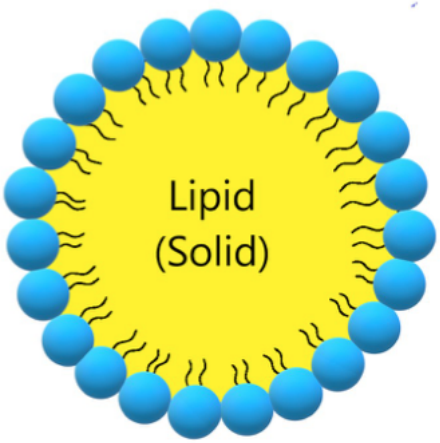

Figure 3. Schematic representation of solid lipid nanoparticle.

3.4. CUR in Nanoemulsions

Nanoemulsions (NE) are thermodynamically stable dispersions of oil and water (Figure 4) [110]. They are formed by a phospholipid monolayer composed of a surfactant and co-surfactant, which are important for nanoemulsion stabilization [110][111]. This system has thermodynamic stability and high solubilization characteristics, with improved drug release kinetics [112]. NE systems can be manufactured through emulsification, which can control the size of the drops and increase the drug solubility and efficacy. Moreover, the main disadvantage of NE is the high amount of surfactants in the formulation, which can lead to a potential toxic effect [111]. Antimicrobials studies with CUR-loaded NE are summarized in Table 4.

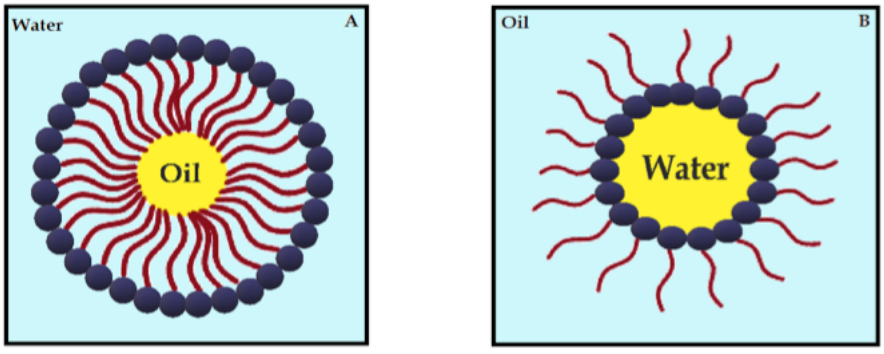

Figure 4. Schematic diagram of oil-in-water nanoemulsion (**A**) and water-in-oil nanoemulsion (**B**), stabilized by surfactants.

Table 4. Antimicrobial studies performed with curcumin/curcuminoid in emulsions.

Type of Emulsion	[CUR] Formulation	Microorganisms	Type of culture	Antimicrobial method	Antimicrobial Concentration	Light/Ultrasonic Paramet	Reference
THC ME	5%	HIV-1	Cell infection	IC_{50}	0.9357 µM	-	[113]

CUR-NE	**N/R**	**HPV**	**-**	**aPDT**	**80 µM**	**50 J/cm^2**	[114]
CUR-NE	**N/R**	**DENV-1 to 4**	**Cell infection**	**Cell viability**	**1, 5, 10 µg/mL**	**-**	[115]
P60-CUR	**4 mg/L**	***E. coli***	**Planktonic**	**OD595 nm**	**N/R**	**-**	[116]
PE:CUR	**0.566 mg/mL**	***S. aureus*, *S. epidermidis*, *S. faecalis*, *C. albicans*, E. coli**	**Planktonic**	**Inhibition zone**	**1 mg/mL***	**-**	[117]
cu-SEDDS	**1%**	***E. aureus*, *E. coli*, *P. aeruginosa*, *K. pneumonia***	**Planktonic**	**MIC**	**45–62 µg/mL**	**-**	[118]
CUR:NE in microbeads	**0.5 mg/mL**	***E. coli*, *S. typhmerium*,*Y. enterocolitica*, *P. aeruginosa*, *S, aureus*, *B. cereus*, *L. monocytogenes***	**Planktonic**	**Inhibition zone**	**90 and 180 mg/mL***	**-**	[119]
Lignin sulfomethylated	**0.3 mg/mL**	***S. aureus***	**Planktonic**	**OD600 nm**	**2.4 mg/mL***	**-**	[120]
C14-EDA/GM/WC14-MEDA/GM/W	**N/R**	***C. albicans***	**Planktonic, biofilm**	**Microdilution assay, antibiofilm**	**100 µg/mL, 20 µg**	**-**	[121]

[CUR]: CUR concentration. -: not performed. N/R: not reported. *: formulation concentration.

3.5. CUR in Cyclodextrin

Cyclodextrins (CDs) have revolutionized the pharmaceutical industry in recent years [122]. 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: 6, 7, or 8 glucose units, which are denominated α-CD, β-CD, and γ-CD, respectively [126][127]. Although the entire CD molecule is soluble in water, the interior is relatively non-polar and creates a hydrophobic microenvironment. Therefore, CDs are cup-shaped, hollow structures with an outer hydrophilic layer and an internal hydrophobic cavity (Figure 5) [126]. They can sequester insoluble compounds within their hydrophobic cavity, resulting in better solubility and consequently better chemical and enzymatic stability [124]. Due to the cavity size, β-CD forms appropriate inclusion complexes with molecules with aromatic rings [128], such as CUR [129]. Antimicrobial studies with CUR in CDs are summarized in Table 5.

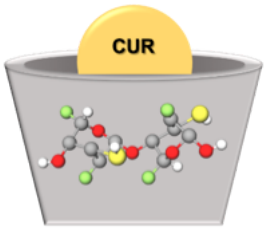

Figure 5. Schematic representation of CUR in CD.

Table 5. Antimicrobial studies performed with CUR in CDs.

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 µM**	***E. coli*, *E. faecalis***	**Planktonic**	**aPDT**	**10 µM**	**4.8, 29 J/cm^2**	[130]
HPMC-stabilized hydroxypropyl-β-CD	**7.64 × 10^{-3} M**	***E. coli***	**Planktonic**	**aPDT**	**10, 25 µM**	**5, 14, 28 J/cm^2**	[131]
methyl-β-CD hyaluronic acid HPMC	**7.64 × 10^{-3} M**	***E. faecalis*, *E. coli***	**Planktonic**	**aPDT**	**0.5–25 µM**	**11, 16, 32 J/cm^2**	[132]
carboxymethyl-β-CD	**20 µM**	***E. coli***	**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**	***S. aureus***	**Planktonic**	**Inhibition zone**	**2% (*w*/*v*)**	**-**	[134]

α- and β-CD	1 mol/L	*E. coli, S. aureus*	Planktonic	MIC, OD600 nm	0.25 and 0.31 mg/mL	-	[135]
β-CD or γ-CD in CS	0.06 mM	*E. coli, S. aureus*	Planktonic	MIC, Zone of inhibition	64 and 32 µg/mL	-	[136]
γ-CD	25 mg/L	*T. rubrum*	Planktonic	MIC, aPDT	N/R	45 J/cm^2	[137]
hydroxypropyl-β-CD	1:1	*B. subtillis, S. aureus, S. pyrogenes, P. aeruginosa, C. difficile, C. butyricum, L. monocytogenes, E. faecalis, E. coli, K. pneumoniae, P. mirabilis, S. typhimurium, E. aerogens, C. kusei, C. albicans*	Planktonic	Inhibition zone	25 mg/mL	-	[138]
methyl-β-CD	20 mM	*E. coli*	Planktonic	MIC, MBC, aPDT	500, 90 µM	9 J/cm^2	[139]

[CUR]: CUR concentration. -: not performed. N/R: not reported.

3.6. CUR in Chitosan

Chitin is a natural polysaccharide commonly found in the exoskeleton of marine crustaceans such as shrimps, prawns, lobsters, and crabs. Chitosan (CS) derives from the acetylation of chitin and has a linear structure of D-glucosamine (deacetylated monomer) linked to N-acetyl-D-glucosamine (acetylated monomer) through β-1,4 bonds [140]. The main advantages that make CS a promising drug carrier include biocompatibility, biodegradability, non-toxicity, controlled release system, mucoadhesive properties, and low cost [140][141]. Moreover, CS is soluble in aqueous solutions and is the only pseudo-natural polymer with a positive charge (cationic) [142], which can interact with negatively-charged DNA, membranes of microbial cells, and biofilm matrix [143]. Antimicrobial studies with CUR in CS are summarized in Table 6.

Table 6. Antimicrobial studies performed with CUR in CS.

Type ofCS	[CUR] Formulation	Microorganism	Type of Culture	Antimicrobial Method	Antimicrobial [CUR]	Reference
PEG-CS	4.4%, 5 mg/mL	MRSA, *P. aeruginosa*	Planktonic, Animal model	OD_{600nm}, CFU	5 and 10 mg/mL *	[144]
CCS microspheres	12.27 mg/mL, 1 mol	*S. aureus, E. coli*	Planktonic	Zone of inhibition, MIC	N/R	[145]
CS nanoparticles	1.06 mg/mL	*S. mutans*	Planktonic, Biofilm	MIC	0.114 mg/mL	[146]
CS-CMS-MMT	0.0004–0.004 g	*S. mutans*	Planktonic, Biofilm	MIC	0.101 mg/mL	[147]
CS-GP-CUR	148.09 ± 5.01 µg	*S. aureus*	Planktonic	Zone of inhibition, tissue bacteria count	N/C	[148]
PVA-CS-CUR	N/C	*E. coli, P. aeruginosa, S. aureus, B. subtilis*	Planktonic	Zone of inhibition	N/R	[149]
PVA-CS-CUR	10, 20, 30 mg	*P. multocida, S. aureus, E. coli, B. subtilis*	Planktonic	Zone of inhibition	10, 20, 30 mg	[150]
CS NPs	2, 4, 8, 16%	*C. albicans, S. aureus*	Planktonic, Biofilm	MIC, Colony count	400 mg/mL	[151]
CS NPs	4 mg/mL	HCV-4	N/R	Antiviral assay	15 µg/mL	[152]
CS/milk protein nanocomposites	100 mg	PVY	Plant infection	Antiviral activity	500, 1000, 1500 mg/100 mL	[153]

[CUR]: CUR concentration. N/R: not reported. N/C: not clear. *: formulation concentration.

3.7. CUR in Other Polymeric DDS

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

Table 7. Antimicrobial studies performed with curcumin in polymeric drug delivery systems.

Type of Polymeric DDS	[CUR] Formulation	Microorganism	Type of Culture	Antimicrobial Method	Antimicrobial [CUR]	Light/Ultrasonic Parameters	Reference
PEG 400γ-CD and PEG + β-CD	0.18%	*E. faecalis, E. coli*	Planktonic	CFU/mL aPDT	N/R	9.7 J/cm^2 29 J/cm^2	[154]
CUR-NP without polymer	100 mg	*S. aureus, B. subtillis, E. coli, P. aeruginosa, P. notatum, A. niger*	Planktonic	MIC Inhibition zone	100 mg, 0.27 mmol	-	[155]
CUR-NP without polymer	100 mg	*M. lutues, S. aureus, E. coli, P. aeruginosa*	Planktonic	MBC	N/R	-	[156]
Mixed polymer NP	5 mM	*E. coli*	Planktonic	MIC	400–500 µM	-	[157]
CTABTween 20Sodium dodecylsulfate	100 mg/mL	*L. monicytogenes*	Planktonic	Inhibition zone	N/R	-	[158]
PLA/dextran sulfate	4 mg/mL	MRSA, *C. albicans, S. mutans*	Planktonic/mono- and –mixed biofilm	aPDT	260 µM	43.2 J/cm^2	[159]
PLA/dextran sulfate	0.4%	*C. albicans*	Animal model	aPDT	260 µM	37.5 J/cm^2	[160]
Nanocurcumin	N/R	*P. aeruginosa* (isolates) and standard strain	Planktonic	MIC	128 µg/mL	-	[161]
PLGA	5 mg	*S. saprophyticus* subsp. *Bovis, E. coli*	Planktonic	aPDT	50 µg/mL	13.2 J/cm^2	[162]
Eudragit L-100	N/C	*L. monocytogenes*	Planktonic	Animal model infection	N/R	-	[163]
nCUR	N/R	*S. mutans*	PlanktonicBiofilm	Inhibition zoneaPDT	N/R	300–420 J/cm^2	[164]
nCUR combined with indocyanine	100 mg	*E. faecalis*	Biofilm	Metabolic activity	N/R	500 mW/cm^2	[165]
PVAc-CUR-PET-PVDC	0.02 g	*S. aureus, S. tiphimurium*	Planktonic	aPDT	N/R	24, 48, and 72 J/cm^2	[166]
MOA.CUR-PLGA-NP	Up to 10%	*S. mutans*	Biofilm	aPDT	7% wt	45 J/cm^2	[167]
CS- β-CD	N/C	*S. aureus, E. coli*	Planktonic	Colony count	Up to 0.03%	-	[168]

[CUR]: CUR concentration. -: not performed. N/R: not reported. N/C: not clear.

3.8. CUR with Metallic Nanoparticles

Metal complexation plays an important role in the therapeutic properties of CUR. The β-diketone moiety in the CUR chemical structure enables it to form complexes with metal ions [169]. A previous review summarized the antimicrobial activity of CUR and curcuminoid complexes with metals, such as boron, Ca^{2+}, Cd^{2+}, Cr^{3+}, Co^{2+}, Cu^{2+}, Fe^{3+}, Ga^{3+}, Hg^{2+}, In^{3+}, Mn^{2+}, Ni^{2+}, Pd^{2+}, Sn^{2+}, Y^{3+}, and Zn^{2+} against viruses, bacteria, and fungi [169]. Metals have also been combined with polymers to improve the biological effects of CUR and to be used as films, hydrogels, dressings, and other pharmaceutical formulations [170][171]. In this context, silver NPs (AgNPs) have been extensively used due to their antimicrobial activity (Figure 6) [172]. Antimicrobial studies with CUR complexes with metals are summarized in Table 8.

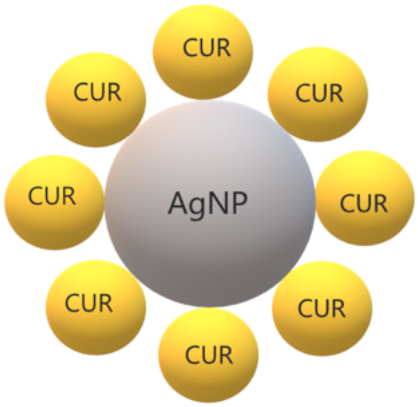

Figure 6. Schematic representation of CUR in silver nanoparticles.

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	*P. aeruginosa*, *E. coli*, *B. subtilis*, *S. aureus*	Planktonic	MIC	20 mg/mL	[173]
Ag-CUR-nanoconjugates	0.1 mM	*E. coli*, *Salmonella* spp., *Fusarium* spp., *S. aureus*	Planktonic	Zone of Inhibition	0.1 mM	[174]
AgCURNPs	500 mg	*P. aeruginosaS. aureus*	Biofilm	CLSM SEM	Up to 400 µg/mL	[175]
AgNPs	7 mg	*E. coli*	Planktonic	Turbidimetric Assay	0.005 µM	[176]
cAgNPs	7 mg	*E. coliB. subtilis*	Planktonic	MIC, CFU/mL	7 mg	[177]
Ru II complex	0.092 g	*E. coli, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa, Enterococcus* sp.	Plakntonic	MIC/FICI	>64 µg/mL	[178]
SCMC SNCF nanocomposites with CUR	0.25 mg/mL	*E. coli*	Planktonic	Disc Method Count Method	2 mg/mL	[179]
CSCL CUR-AgNP	0.092 g	*E. coli*, *B. subtilis*	Planktonic	Zone of Inhibition	10 and 20 µM	[180]
nSnH	10%	*S. aureus, E. coli*.	Planktonic	CFU/mL	N/R	[181]
Nanocomposite of CUR and ZnO NPs	N/C	*S. epidermidis, S. hemolyticus, S. saprophyticus*	Planktonic	Zone of Inhibition	1000, 750, 500, 250 µg/mL	[182]
Thermo-responsive hydrogels	N/C	*S. aureusP. aeruginosaE. coli*	Planktonic	MIC	400 µg/mL	[183]
CUR-AgNPs	5 mg/mL	*C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, C. krusei, C. kefyr*	Planktonic	Zone of Inhibition, MIC	32.2–250 µg/mL	[184]
Gel-CUR-Ag	20 mg	*P. aeruginosa, S. aureus*	Planktonic	MIC, MBC	20 mg	[185]
HGZ-CUR	N/C	*S. aureus, T. rubrum*	Planktonic	Zone of Inhibition	N/C	[186]
CHG-ZnO-CUR	N/C	*S. aureus, T. rubrum*	Planktonic	Zone of Inhibition	N/C	[187]
Copper (II) oxide NPs	1 g	*E. faecalis, P. aeruginosa*	Planktonic	Zone of Inhibition CFU/mL	1 mg/mL	[188]
OA-Ag-C	1 g	*P. aeruginosa, S. aureus*	Planktonic	OD_{600nm}	2.5 mg/mL	[189]
Ag-NP-β-CD-BC	0.79 g	*P. aeruginosa, S. aureus, C. auris*	Planktonic	Zone of Inhibition	N/R	[190]

Cotton fabrics coated ZnO-NP	2.71 × 10^{-3} M	*S. aureus, E. coli*	Planktonic	Bacterial Count	N/R	[191]
CS-ZnO-CUR	0.2 g	*S. aureus, E. coli*	Planktonic	MIC, MBC	Up to 50 µg/mL	[192]
CUR-TiO_2 -CS	100–300 mg	*S. aureus, E. coli*	Planktonic Animal infection	MIC	10 mg	[193]
CUR-Au-NPs	1 mg/mL	*E. coli*, *B. subtilis*, *S. aureus*, *P. aeruginosa*	Planktonic	Zone of Inhibition	100, 200, 300 µg/mL	[194]

[CUR]: CUR concentration. N/R: not reported. N/C: not clear.

3.9. CUR in Mesoporous Particles

Porous materials are structures with ordered pores ranging from nanometer to micrometers, which are classified as microporous (less 2 nm), mesoporous (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, Figure 7) are inorganic scaffolds [197], which seemed ideal carriers for hydrophobic drugs due to their well-defined structure, large specific surface area, and versatile chemistry for functionalization [198]. The pore size and volume 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 environmental stimuli, such as pH, temperature, or light. These stimuli-responsive DDS, or smart DDS, prevent undesirable drug release before reaching the target tissue ("zero premature release") [199]. Antimicrobial studies with CUR in porous DDSs are summarized in Table 9.

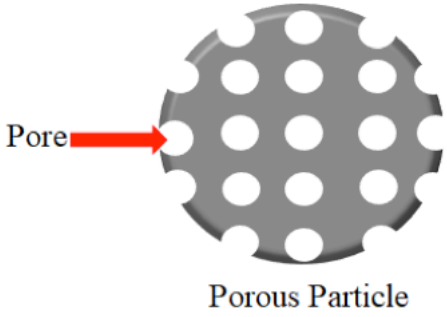

Figure 7. Schematic representation of a porous particle.

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

Porous DDS	[CUR] Formulation	Microorganism	Type of Culture	Antimicrobial Method	Antimicrobial [CUR]	Light/Ultrasonic Parameters	Reference
Cu-SNP/Ag	1.0 mmol	*E. coli*	Planktonic	aPDT	N/R	72 J/cm^2	[200]
Bionanocomposite silica/chitosan	100 mg	*E. coli, S. aureus*	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}	*E. coli, S. aureus*	Planktonic	OD_{600nm}	N/R	-	[203]
SBA-15/PDA/Ag	2 mg	*E. coli, S. aureus*	Planktonic	CFU/mL	50 mM	-	[204]

[CUR]: CUR concentration. -: not performed. N/R: not reported.

3.10. CUR in Quantum Dots

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 carbon material and molecular precursors, respectively [205]. Antimicrobial studies with CUR in QDs are summarized in Table 10.

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

Type of Material	[CUR] Formulation	Microorganism	Type of Culture	Antimicrobial Method	Antimicrobial [CUR]	Light/Ultrasonic Parameters	Reference

CUR-cQDs	0.6	*S. aureus* MRSA *E. faecalis* *E. coli* *K. pneumoniae* *P. aeruginosa*	Planktonic Biofilm	Grown inhibition Biomass evaluation Confocal microscopy	3.91–7.825 µg/mL	-	[206]
CUR-cQDs	200 mg	EV-71	Cell infection Animal infection	MIC Plaque assay TC IC50 assay Western blot PCR	5 µg/mL	-	[207]
CUR-MQD	2:1 wt%	*K. pneumoniae* *P. aeruginosa* *S. aureus*	Planktonic	MIC MBC Confocal microscopy Fluorescence microscopy Flow cytometry	<0.00625–0.125 µg/mL	-	[208]
CUR-GQDs	N/C	A. actinomycetemcomitans P. gingivalis P. intermedia	Mixed biofilm	aPDT	100 µg/mL	60–80 J/cm2	[209]

3.11. CUR in Films, Hydrogels, and Other Nanomaterials

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

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

Type of Material	[CUR] Formulation	Microorganism	Type of Culture	Antimicrobial Method	Antimicrobial [CUR]	Light/Ultrasonic Parameters	Reference
CuR-SiNPs	20 mg	*S. aureus, P. aeruginosa*	Planktonic, Biofilm	aPDT	50 µg/mL, 1 mg/mL	20 J/cm^2	[210]
CUR-HNT-DX	10 mg	*S. marcescens, E. coli*	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]
Electrospun nanofibers	100 mg/mL	*Actinomyces naeslundii*	Biofilm	aPDT	2.5 and 5 mg/mL	1200 mW/cm^2	[213]
Ga NFCD-GO NF	0.1 mol	*B. cereus, E. coli*	Planktonic	Zone of inhibition, MIC	Up to 63.25 µg/mL	-	[214]
Multinanofibers-film	1, 2.5, and 5 mg/mL	*S. aureusE. coli*	Planktonic	UFC/mL, Confocal microscopy	1 mg/mL	-	[215]
Nanofibers scaffolds	4.0 wt%	*S. aureus Pseudomonas*sp.	Planktonic	Colony count	N/R	,-	[216]
Nanofibrous scaffold	5%	*S. aureus, E. coli*	Planktonic	Colony count	20 mg	-	[217]
Nanofibers	5 and 10%wt	*S. aureusE. coli*	Planktonic	OD_{600nm}	Up to 212.5 µg/mL	-	[218]
CSDG	1 w/w	*S. aureus, E. coli*	Planktonic, Infection model	Colony count, Microscopy	N/R	-	[219]
Gelatin film	0, 0.25, 0.5, 1.0, and 1.5 wt%	*E. coli, L. monocytogenes*	Planktonic	UFC/mL	0.25 and 1.5 wt%	-	[220]
ZnO-CMC film	0.5 and 1.0 wt%	*E. coli, L. monocytogenes*	Planktonic	UFC/mL	1 wt%	-	[221]
Pectin film	40 mg	*E. coli, L. monocytogenes*	Planktonic	UFC/mL	N/R	-	[222]
Edible film	0.4% (*w*/*v*)	*E. coli, B. subtilis*	Planktonic	Zone of inhibition	1% wt.	-	[223]

[CUR]: CUR concentration. -: not performed. N/R: not reported. N/C: not clear

4. Conclusions and Future Perspectives

CUR has a broad-spectrum antimicrobial activity against viruses, bacteria, and fungi, including resistant and emergent pathogens. However, some species such as Gram-negative bacteria are less susceptible to CUR and aPDT. For those, the combination of CUR with antibiotics has been suggested, especially for antibiotic-resistant strains [220]. CUR showed synergism with polymyxin and protection against the side effects of polymyxin treatment, nephrotoxicity, and neurotoxicity [224]. Nonetheless, the evaluation of synergism requires accurate methods to study drug interaction, considering potential differences between the dose–response relationship of individual drugs and avoiding over- or under-estimation of interactions. For example, while the time–kill curve of *C. jejuni* treated with 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 FICI method was not able to detect the synergism between binary combinations of antimicrobials (cinnamon oil, ZnO NPs, and CUR encapsulated in starch) at sub-MIC, which resulted in the non-turbidity of *C. jejuni*. In turn, mathematical modeling using isobolograms and median-effect curves showed synergism when CUR in starch was combined with other antimicrobials against *C. jejuni*, with bacterial reductions of 3 log for the binary combination and over 8 log for the tertiary combination. The mathematical modeling suggested that CUR in starch was the main 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.

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