Curcumin as an Antibacterial Agent

Subjects: Allergy

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The rapid spread of antibiotic resistance and lack of effective drugs for treating infections caused by multi-drug resistant bacteria in animal and human medicine have forced us to find new antibacterial strategies. Natural products have served as powerful therapeutics against bacterial infection and are still an important source for the discovery of novel antibacterial drugs. Curcumin, an important constituent of turmeric, is considered safe for oral consumption to treat bacterial infections. Many studies showed that curcumin exhibited antibacterial activities against Gram-negative and Gram-positive bacteria. The antibacterial action of curcumin involves the disruption of the bacterial membrane, inhibition of the production of bacterial virulence factors and biofilm formation, and the induction of oxidative stress. These characteristics also contribute to explain how curcumin acts a broad-spectrum antibacterial adjuvant, which was evidenced by the markedly additive or synergistical effects with various types of conventional antibiotics or non-antibiotic compounds.

Keywords: antibacterial resistance ; curcumin ; bacterial infection ; molecular mechanism ; nano-formulations

1. Antibacterial Activity of Curcumin

In 1949, Schraufstatter and colleagues were the first to report the antibacterial properties of curcumin [1]. In the past seventy years, there have been several studies of the broad-spectrum inhibitory effect that curcumin exhibits against various Gram-negative and Gram-positive bacteria, including *A. baumannii, E. faecalis, K. pneumoniae, P. aeruginosa, Bacillus subtilis (B. subtilis), Staphylococcus epidermidis, Bacillus cereus (B. cereus), Listeria innocua, Streptococcus pyogenes, S. aureus, Helicobacter pylori (H. pylori), Escherichia coli (E. coli), Salmonella enterica* serotype Typhimurium, and *Streptococcus mutans* (Details shown in **Table 1**) [2][3][4][5][6]. Importantly, curcumin also exhibits marked antibacterial activities against MDR-isolates, such as polymyxin-resistant *K. pneumoniae* and MRSA [7][4][6]. A recent study by Batista de Andrade Neto et al., reported that minimum inhibitory concentration (MIC) values for curcumin against clinical isolates of MRSA were in the range of 125–500 µg/mL [8]. Another study by Yasbolaghi Sharahi et al., reported that MICs of curcumin against MDR-*A. baumannii, P. aeruginosa* and *K. pneumoniae* were in the range of 128–512 µg/mL [3]. Notably, there were significant differences in the MICs of curcumin against certain stains reported by different research groups [9]. This may be due to the difference in solubility of curcumin in the different vehicles (e.g., water, DMSO, and ethanol) used by each research group [9]. In addition, these differences may be related to the MIC test methodology, impact of the vehicle against the bacterial outer membrane, and purity of the curcumin used in the research [10].

Table 1. Documented antibacterial activities of curcumin.

Bacteria Type	Antibacterial Activity	References
Staphylococcus aureus	**Growth inhibition, inhibition of cell division or biofilm formation inhibition**	[11][12][13]
Staphylococcus epidermidis	**Growth inhibition or biofilm formation inhibition**	[14]
Streptococcus pyogenes	**Growth inhibition**	[15]
Bacillus subtilis	**Growth inhibition, or cell division inhibition**	[5][11][13][16]
Bacillus cereus	**Growth inhibition, or biofilm formation inhibition**	[17][18]
Listeria innocua	**Growth inhibition**	[19]
Helicobacter pylori	**Growth inhibition**	[20][21][22]
Pseudomonas aeruginosa	**Growth inhibition, biofilm formation inhibition, or inhibition of cell division**	[11][12][13][16]
Escherichia coli	**Growth inhibition, biofilm formation inhibition, or inhibition of cell division**	[3][11][13][16]

Bacteria Type	Antibacterial Activity	References
Streptococcus mutans	**Adhesion inhibition, biofilm formation inhibition**	[23]
Salmonella entericaserotype Typhmurium	**Growth inhibition, or inhibition of surface motility**	[24][25]
Klebsiella pneumoniae	**Growth inhibition**	[3][7][16]
Acinetobacter baumannii	**Growth inhibition, biofilm formation inhibition or inhibition of the surface motility**	[3][26]
Enterococcus faecium	**Growth inhibition**	[3][11][16]
Mycobacterium abscessus	**Growth inhibition, or biofilm formation inhibition**	[27]
Porphyromonas gingivalis	**Growth inhibition, or biofilm formation inhibition**	[28]
Clostridium difficile	**Growth inhibition**	[29]

2. Synergistic Antibacterial Effects of Curcumin with Antibacterial or Non-Antibacterial Agents

Synergistic antibacterial effects between antibiotics are strictly defined microbiological phenomena, requiring two bioactive agents to exhibit a greater effect in bacterial killing than the added effects of each constituent [30].

Several studies have shown that curcumin exhibits synergistic antibacterial effects when combined with traditional antibacterial agents (e.g., polymyxins, meropenem, oxacillin, tetracycline, ciprofloxacin, ampicillin, norfloxacin), natural products (e.g., epigallocatechin gallate, berberine) or metals (e.g., Cu^{2+}, Zn^{2+}, and Fe^{3+}) [31][32][33][34]. In the proceeding discussion, there is a summarization of these potential combinations and a discussion of their various mechanisms of action.

2.1. Synergistic Effect between Curcumin and Antibacterial Agents

2.1.1. Curcumin and Polypeptide Antibacterial Drugs

In the clinic, vancomycin and polymyxins (including polymyxin B and E, also called colistin) are commonly employed as antibacterial drugs against MDR Gram-negative and Gram-positive bacteria, respectively [35]. The emergence of polymyxin- and vancomycin-resistant bacteria has posed a huge challenge and medical burden.

The well-accepted primary mechanism of action of polymyxins is through spatially displacing the cations (e.g., Ca^{2+} and Mg^{2+}) in the Gram-negative outer membrane and binding to the lipid A component of the lipopolysaccharide (LPS), subsequently disrupting the stability of both the outer and inner membranes, ultimately leading to bacterial cell lysis [36]. Recent studies also indicated that polymyxins can also induce the production of excessive ROS (i.e., $OH^{\bullet}$) in bacterial cells, leading to oxidative stress-dependent cell death [37]. Polymyxin B in combination with curcumin showed a marked synergetic effect against polymyxin-susceptible and -resistant Gram-positive (e.g., *Enterococcus, S. aureus,* and *Streptococcus*) and Gram-negative (e.g., *A. baumannii, E. coli, P. aeruginosa,* and *S. maltophilia*) bacterial isolates associated isolated from traumatic wound infections [15]. This synergistic effect may be due to curcumin's ability to permeabilize the outer membrane, which facilitates the entry of the secondary agent to enter the bacterial cells and cause cell death [6]. In addition, this synergistic effect could be attributed to the inhibitory effect of curcumin on the activities of efflux pumps [7][6]. Curcumin and polymyxin combination treatment for bacterial infections may have another advantage, i.e., significant improvement in the therapeutic index of polymyxins by additionally inhibiting polymyxin-induced cytotoxicity, neurotoxicity, and nephrotoxicity, which is beyond antibacterial activity [38]. This combination may have a powerful application in clinical practice and warrants clinical trials.

Vancomycin is a glycopeptide antibiotic that inhibits a specific step in the synthesis of the peptidoglycan layer in Gram-positive bacteria. It has been reported that curcumin combined with vancomycin showed a synergistic effect against MDR clinical *K. pneumoniae* isolates [39]. This potential mechanism may be dependent on the synergistic effect of cell membrane permeability [39]. Moreover, curcumin could also attenuate vancomycin-induced nephrotoxicity by inhibiting oxidative stress and the inflammation response in a rat model [39].

2.1.2. Curcumin and β- Lactam Antibacterial Drugs

β-lactam antibiotics are the most widely used antibacterial agents worldwide. β-lactamases confer significant antibiotic resistance to their bacterial hosts by hydrolyzing the amide bond of the four-membered β-lactam ring of β-lactam antibiotics, which include four classes of drugs, i.e., penams (penicillins), cephems (cephalosporins), monobactams, and carbapenems [40]. It has reported that a curcumin and meropenem combination displayed markedly synergistic or additive effects against antibiotic-susceptible and -resistant Gram-positive (*E. faecalis*) and carbapenem-associated MDR *A. baumannii, P. aeruginosa*, and *K. pneumoniae* isolates via the observation of MICs [31]. A report by Yadav et al., showed that a water-soluble curcumin derivative could reverse meropenem resistance by targeting the activity of carbapenemases and the AcrAB-TolC multidrug efflux pump system [41]. Mun et al. showed that a curcumin combination with oxacillin and ampicillin exhibited a marked synergistic effect against *S. aureus* ATCC (American Type Culture Collection) 25,923 (methicillin-sensitive strain) [42]. Similarly, in another study, BDMC in combination with oxacillin showed a marked synergistic effect against *S. aureu* ATCC 33,591 (methicillin-resistant strain) and clinical MRSA isolates [43]. The potential mechanism may be dependent on the expression of the mecA gene that encodes penicillin-binding protein 2a (PBP2a), which governs the resistance of MRSA isolates to β-lactam antibiotics [43]. Sasidharan et al. found that curcumin in combination with third-generation cephalosporins (e.g., cefaclor, cefodizime, and cefotaxime) showed marked synergistic effect against *S. aureus*, *B. subtilis,* and *E. coli*, which are also associated with infectious diarrhea [32]. There was no increased toxic effects between these combinations [32]. These results indicated curcumin and cephalosporin combination are promising therapeutic options for infectious diarrhea disease.

2.1.3. Curcumin and Aminoglycoside Antibacterial Drugs

Aminoglycosides are potent, broad-spectrum antibiotics that act through inhibition of protein synthesis by irreversibly binding to 30S ribosomal subunits [44]. A report by Teow et al., stated that curcumin in combination with two aminoglycoside antibiotics (e.g., amikacin and gentamicin) showed a powerful synergistic effect against *S. aureus* strains, and these synergistic effects were stronger than that of curcumin in combination with ciprofloxacin [45]. Notably, this difference in synergistic effect may be related to the difference in the primary targets between quinolone and aminoglycosides against bacteria [46]. The potential action mechanism is related to the inhibition of biofilm formation, which was evident by the significant inhibition of their combination of the swarming motilities and the mRNA expression of several key QS regulatory genes (e.g., lasI, lasR, rhlI, and rhlR) [45]. In addition, it has been reported that curcumin can also attenuate gentamicin-induced nephrotoxicity and neurotoxicity by inhibiting oxidative stress and cell apoptosis in a rat model [47]. Therefore, the combination between curcumin and aminoglycosides can not only improve the antibacterial effectiveness but can also decrease the toxic effects of gentamicin.

2.1.4. Curcumin and Macrolide Antibacterial Drugs

Azithromycin is a macrolide antibiotic, which can exhibit a good antibacterial effect by inhibiting bacterial protein synthesis, quorum-sensing, and the formation of biofilms. In clinical practice, azithromycin has been used in treating respiratory, urogenital, dermal, and other bacterial infections [48]. Bahari et al., found that curcumin in combination with azithromycin showed a synergistic effect against *P. aeruginosa* PAO1, and the value of FICI was 0.25 [45]. The potential action mechanism may be similar to the above-mentioned combination of curcumin and gentamicin [45]. Erythromycin is in a class of medications called macrolide antibiotics. The action mechanism involves the blockade of bacterial growth. In a rat model, oral administration of curcumin (50 mg/kg) and erythromycin (20 mg/kg) significantly inhibited the growth of MRSA isolates in bone tissue compared to either administered alone [49]. The curcumin and erythromycin combination also significantly alleviated bone infection and the inflammatory response [49].

2.1.5. Curcumin and Quinolone Antibacterial Drugs

There was a marked synergistic effect in curcumin combination with two quinolone antibiotics (e.g., ciprofloxacin and norfloxacin) against the *S. aureu* ATCC 33,591 strain and clinical MRSA isolates [42]. On the contrary, curcumin treatment reduced the antimicrobial activity of ciprofloxacin against *Salmonella typhimurium* and *Salmonella typhi* [42]. This may be related to the antioxidant property of curcumin and its inhibition of the expression of interferon γ (IFNγ) in vitro and in a mouse model [42].

2.2. Curcumin and Natural Products

2.2.1. Curcumin and Berberine

Berberine is a benzylisoquinoline alkaloid compound and has antimicrobial properties against both Gram-negative and Gram-positive bacteria [50]. Berberine has been widely used in traditional Chinese and native American medicines. FtsZ protein is an important target of berberine in inhibiting bacterial division [51]. Interesting, co-encapsulation of berberine and curcumin in liposomes decreased their MICs against MRSA by 87% and 96%, respectively, as compared to their free forms, with an FICI of 0.13, indicating a synergistic effect [33]. However, the synergistic effect in their combination in native

form was not detected. In addition, co-treatment of berberine and curcumin in liposomes also significantly improved intracellular infection and the inflammation response in macrophages following MRSA infection. Mechanically, the synergistic effect between curcumin and berberine is partly dependent on the inhibition of biofilm formation and improvement of their solubilities [33]. Additionally, similar to curcumin, berberine is also an FtsZ inhibitor and inhibits bacterial cell division [50]. Therefore, this synergistic effect between curcumin and berberine may also be partly dependent on the inhibition of FtsZ assembly.

2.2.2. Curcumin and Epigallocatechin Gallate

Epigallocatechin-3-gallate (EGCG) is a polyphenol found in green tea, which, similar to curcumin, has been linked with health benefits and has significant antimicrobial activity against some MDR pathogens, including MDR *S. maltophilia*, *A. baumannii,* and *S. aureus* [52]. In vitro, it has been found that curcumin in combination with EGCG exhibited a marked synergistic effect against MDR *A. baumannii* [53]. A possible explanation for the synergy between curcumin and EGCG could be disruption of the outer membrane and facilitation of curcumin to enter bacterial cells [54]. In another study, it was suggested that inhibition of acylhomoserine lactone-mediated biofilm formation may contribute to this synergistic effect, and investigations of precise mechanisms are still required [55].

2.3. Curcumin and Metals

Many metals have been used as antimicrobial agents due to the antiquity and potential molecular mechanism involved in oxidative stress, protein dysfunction or membrane damage in bacterial cells [56]. A copper (II) sulfate pentahydrate–curcumin complex (Cu-CUR), iron (III) nitrate nonahydrate–curcumin complex (Fe-CUR), and zinc (II) chloride–curcumin complex (Zn-CUR) all significantly inhibited cell growth in *P. aeruginosa* PAO1 compared to curcumin treatment alone [57] [58]. Furthermore, the authors found that the Cu–CUR complex significantly inhibited the formation of the biofilm and the production of QS-related virulence factors of *P. aeruginos* PAO1 [34]. Consistently, the synergistic activity of curcumin and silver/copper nanoparticles (NPs) was detected against the cell growth and biofilm formation of *S. aureu* and *P. aeruginosa* compared to curcumin, AgNPs or CuNPs alone [59]. These marked synergistic effects may be related to the improvement of curcumin or intracellular uptake of curcumin [60].

3. Conclusions and Perspectives

Animal experiments and human clinical trials reveal that curcumin has high safety. However, unlike curcumin as a chemotherapy drug in cancer therapy, curcumin as a potential antibacterial therapy still has many challenges: (1) the critical targets of curcumin alone or combination in bacteria and precise molecular mechanisms are poorly understood; (2) the poor solubility, low bioavailability, and rapid degradation in humans or animals when curcumin was consumed orally; (3) no effective clinical trials. In order to overcome the poor solubility of curcumin, scientists have developed various curcumin nano-formulations and they indeed exhibited better solubility and antibacterial activity compared to native curcumin. However, there is a lack of evidence-based randomized investigation especially exploring the therapeutic roles of the nanocarrier-based delivery systems in enhancing anti-bacterial actions; therefore, much needs to be explored.

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