

Review Article

Antibacterial Action of Curcumin against *Staphylococcus aureus*: A Brief Review

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Curcumin, the major constituent of *Curcuma longa* L. (Zingiberaceae family) or turmeric, commonly used for cooking in Asian cuisine, is known to possess a broad range of pharmacological properties at relatively nontoxic doses. Curcumin is found to be effective against *Staphylococcus aureus* (*S. aureus*). As demonstrated by *in vitro* experiment, curcumin exerts even more potent effects when used in combination with various other antibacterial agents. Hence, curcumin which is a natural product derived from plant is believed to have profound medicinal benefits and could be potentially developed into a naturally derived antibiotic in the future. However, there are several noteworthy challenges in the development of curcumin as a medicine. *S. aureus* infections, particularly those caused by the multidrug-resistant strains, have emerged as a global health issue and urgent action is needed. This review focuses on the antibacterial activities of curcumin against both methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA). We also attempt to highlight the potential challenges in the effort of developing curcumin into a therapeutic antibacterial agent.

1. Introduction

Curcumin or diferuloylmethane is the major phytochemical of *Curcuma longa* L. (Zingiberaceae family), which is commonly known as turmeric. Curcumin is the polyphenolic compound that gives the yellow colour of the herb. Turmeric is mainly cultivated in tropical and subtropical regions and is mainly produced by India. Traditionally, it has been used to flavour food, dye cloths, and treat various human ailments [1]. Curcumin is extracted from turmeric by solvent extraction (preferably with ethanol) through various methods (e.g., Soxhlet, ultrasonic, microwave, and supercritical carbon dioxide) followed by purification via column chromatography [2, 3]. Ever since the identification of curcumin as the main constituent of turmeric, multiple pharmacological activities of curcumin that include antimicrobial, antidiabetic,

anti-inflammatory, anticancer, and antioxidant have been reported [4–6]. More excitingly, when combined with other drugs, curcumin has been found to enhance the effects of antibacterial [7–9], antifungal [10, 11], anticancer [12, 13], and antioxidant [14, 15] activities.

Curcumin usually exhibits low to no toxicity at the active doses. A systematic review from the MEDLINE computerized database (1966 to 2002) has shown that curcumin is safe when consumed up to 8 g each day consecutively for 3 months in a phase I human trial that involved 25 subjects [16]. Similarly, the dose of 8 g per day was safe when used in combination with gemcitabine that showed marked therapeutic effects in pancreatic cancer patients [17, 18]. Interestingly, curcumin is also able to reverse the Aflatoxin B1-induced toxicity and iron-overloaded liver toxicity in rats [19–21]. Despite being extensively studied, the exact mechanism(s) of curcumin's

multiple biological and pharmacological activities remains to be explored. Based on the available literature, there are two hypotheses describing the poly-pharmacological effects of curcumin. First, curcumin is known to act on multiple targets [4, 5, 22–24], hence having diverse roles in regulating various cellular processes. Secondly, products resulting from the curcumin degradation have been shown to be highly diverse depending on the chemical or biochemical reactions involved [25–27]. Most of these products are stable and function differently that may lead to the multiple effects.

The most studied activity of the curcumin in the past 10 years is the anticancer effects [28]. However, the first paper describing the biological action of curcumin was its antibacterial activity against various bacteria: *S. aureus*, *Trichophyton gypseum*, *Salmonella paratyphi*, and *Mycobacterium tuberculosis* [29]. To date, studies on the antibacterial activity of curcumin that indicate inhibition properties of a wide range of bacteria are increasingly documented [6, 23, 30]. Recent publications have also reported that curcumin is active against a plethora of drug-resistant bacterial strains [8, 9, 31, 32]. *S. aureus* infection is a major problem in many developing countries, especially in hospitals where the MRSA spreading is difficult to control [33]. Over the years, the multi-drug-resistant *S. aureus* infection has increased the global morbidity and mortality [34, 35]. Due to the difficulty in treating the infection, it has consequently imposed an elevating burden on healthcare resources [36–38]. Cumulative findings in recent years have shown that curcumin is active against both MSSA and MRSA [8, 9, 30, 32, 39, 40]. In view of the need for a more efficacious and safe therapeutic modality towards the drug-resistant *S. aureus*, we discuss the reported antibacterial activities of curcumin against *S. aureus* and its potentials and limitations to be developed into a potent antibiotic.

2. Curcumin-Mediated Inhibition of *S. aureus*

Curcumin inhibits the growth of both Gram-positive and Gram-negative bacteria [6, 23, 30]. *S. aureus* is one of the Gram-positive strains that is susceptible to curcumin-mediated inhibition. *S. aureus* is a pathogen that causes various infections including infective endocarditis (IE), bacteremia, skin and soft tissue, osteoarticular, and pleuropulmonary infections [33]. Over the years, *S. aureus* has evolved and developed multiple strategies to evade human immune system and to resist antibiotics treatment. This has given rise to the evolution of MRSA, and the emergence of healthcare-associated (HA) and community-associated (CA) MRSA has caused a major problem to the human society [45, 46]. In this section, we discuss the past and current works that show the curcumin-mediated killings of MSSA and MRSA (summarized in Table 1).

Mun et al. [9] showed that the minimal inhibitory concentrations (MICs) of curcumin against 10 strains of *S. aureus* (including 2 ATCC MSSA and MRSA standard strains, 4 MRSA clinical isolates, and 4 MRSA from culture collection) ranged from 125 to 250 $\mu\text{g}/\text{mL}$ while a study by Wang et al. [40] showed the MIC of 256 $\mu\text{g}/\text{mL}$ against MSSA. Using a broth microdilution assay, our group [8] also showed that

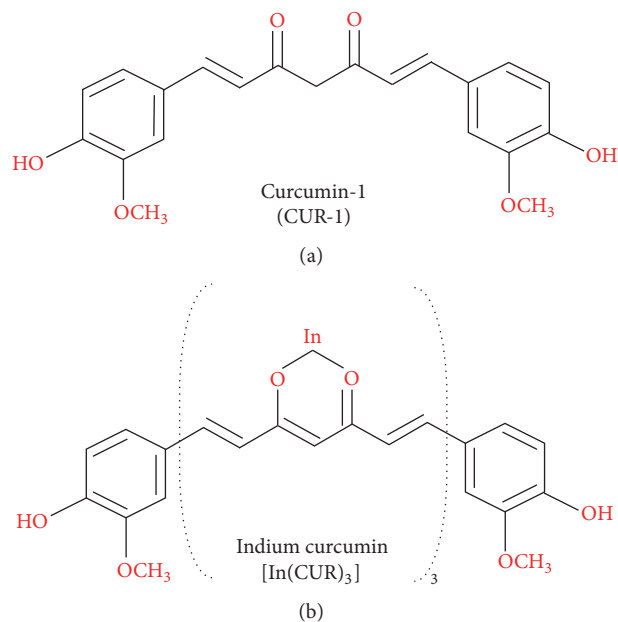


FIGURE 1: Chemical structures of antibacterial curcumin analogues against *S. aureus*. Upper panel shows the structure of curcumin-1 [30, 41] while the lower panel shows the metal complexes of curcumin, indium curcumin [42, 43]. The chemical structures above were drawn using a free online tool, ChemWriter (<http://chemwriter.com/>).

250 $\mu\text{g}/\text{mL}$ curcumin was required to kill the two ATCC MSSA (#25923) and MRSA (#43300) strains. However, another study demonstrated that the MICs against the ATCC standard MSSA and MRSA were 219 and 217 $\mu\text{g}/\text{mL}$, respectively, that are slightly lower than the former study [47]. Recently, Kali et al. [48] showed the mean curcumin MIC of 126.9 $\mu\text{g}/\text{mL}$ against 15 Gram-positive bacterial isolates including thirteen *S. aureus* and two *Enterococcus faecalis*. Nonetheless, this study is not used for comparison in Table 1 because the obtained MIC might not be representative for curcumin's effect against *S. aureus* as the study was carried out in combination with *Enterococcus faecalis*.

A more potent inhibition was achieved when curcumin-1 (CUR-1), a major component of commercial preparations of curcumin (purity > 98%), was used against *S. aureus*. The chemical structure of curcumin-1 is shown in Figure 1. Tyagi et al. [30] showed that the curcumin-1 was active against MSSA at concentration of as low as 25 μM (equivalent to 9.21 $\mu\text{g}/\text{mL}$), as it killed 50% of the bacteria after 2 hr incubation. The activity was time- and dose-dependent, and 100% killing was achieved at 50 μM (equivalent to 18.42 $\mu\text{g}/\text{mL}$) after 2 hr exposure [30]. In contrast, Sasidharan et al. [41] showed that the same compound had a MIC of 250 $\mu\text{g}/\text{mL}$ against *S. aureus*, which is comparable to the native curcumin [8, 9]. In an *in vivo* mouse model, administration of 100 mg/kg curcumin was shown to protect the mice infected with both MSSA and MRSA from pneumonia by targeting the α -hemolysin (H1a) protein of *S. aureus* [40]. In summary, the curcumin MICs against *S. aureus* ranged from 18.42 to 256 $\mu\text{g}/\text{mL}$ (refer to Table 1). The variation could be due to

TABLE 1: Antibacterial activity of curcumin against *S. aureus*.

Compound (solvent)	MIC ($\mu\text{g}/\text{mL}$)	<i>S. aureus</i> strain	Test method	Reference
Curcumin (DMSO)	187.5	MSSA (ATCC 25923)	Broth macrodilution	[42]
Indium curcumin (DMSO)	93.8			
Curcumin (DMSO)	125–250	MSSA (ATCC 25923) MRSA (ATCC 33591) MRSA (4 Clinical isolates) MRSA (4 from CCARM) [#]	Broth microdilution	[9]
Curcumin-1 (DMSO)	250	MSSA (MTCC 902) [*]	Broth microdilution	[41]
Curcumin (DMF)	250	MSSA (ATCC 25923) MRSA (ATCC 43300) MSSA (1 Clinical isolates) MSSA (10 Env. isolates)	Broth microdilution	[8]
Curcumin-1 (DMSO)	18.42	MSSA (ATCC 29213)	Colony counting method	[30]
Curcumin (ethanol)	219	MSSA (ATCC 29213)	Broth macrodilution	[47]
	217	MRSA (ATCC 43300)		
Curcumin (ethanol)	125	MSSA (ATCC 25923)	Broth macrodilution	[49]
Curcumin (DMSO)	256	MSSA (USA 300) MSSA (8325-4)	Broth microdilution	[40]

[#]CCARM: culture collection of antimicrobial resistant microbes.

^{*}Purchased from Microbial Type Culture Collection Centre (MTCC), IMTECH, Chandigarh, India.

Env.: environmental.

(i) strain difference (i.e., MRSA versus MSSA); (ii) source of bacterial strains (i.e., ATCC standard strains versus clinical isolates); (iii) type of antibacterial assay (i.e., disk diffusion versus broth microdilution); and (iv) type of curcumin and its solvent (i.e., commercial compound versus in-house purified compound). Overall, the cumulative findings showed that there is no difference of MICs against MSSA and MRSA, suggesting that the sensitivity towards curcumin treatment is not altered by the multidrug resistance machinery in *S. aureus*.

There have been several explanations on how curcumin acts and kills the bacteria which are illustrated in Figure 2. Rai et al. [44] have demonstrated that curcumin interacts with FtsZ (prokaryotic homologue of eukaryotic cytoskeletal protein tubulin) *in vitro* and inhibits the assembly of FtsZ protofilaments in *Bacillus subtilis* 168. Although it has not been examined directly on *S. aureus*, it is believed that inhibiting the assembly dynamics of FtsZ is one of the main mechanisms of curcumin in inhibiting bacterial cell proliferation. FtsZ is also believed to be a novel target for the development of antibacterial drugs against *S. aureus*. [63, 64]. Mun et al. [32] showed that the antibacterial action of curcumin against both MSSA and MRSA was markedly enhanced when used in combination with ATPase inhibitors and mild detergents that compromise ATP-binding cassette (ABC) transporters and cytoplasmic membrane integrity, respectively. The same study has also shown that curcumin binds to peptidoglycan (PGN), and the increasing concentrations of PGN block the curcumin antibacterial activity. Tyagi et al. [30] also showed that curcumin-1 inhibited *S. aureus* growth by perturbing the bacterial membrane integrity. In this study, the bacterial membrane of *S. aureus* was examined using two fluorescent probes: propidium iodide and calcein. The membrane

leakage upon exposure to curcumin was also evaluated by fluorescence and scanning electron microscopies. Although existing evidence suggests that curcumin inhibits *S. aureus* mainly by damaging the bacterial membrane, further investigation is required to identify additional bacterial target proteins besides FtsZ and PGN. This is important not only to enhance the understanding of the curcumin interaction with its target proteins, but also to further improve the activity of curcumin against *S. aureus*, particularly the MRSA strains. Similar studies should also be performed on the curcumin derivatives such as curcumin-1 (curcumin with highest purity >98%) and indium curcumin (metal complex with curcumin) which have shown more potent antibacterial effects than the native curcumin. The chemical structures of curcumin-1 and indium curcumin are shown in Figure 1.

3. Synergism of Curcumin with Antibiotics against *S. aureus*

In addition to showing potent antibacterial activity when used alone, curcumin also exerts marked activity against *S. aureus* when used at subinhibitory dose in combination with various other antibiotics [8, 9, 31, 32]. These findings are interesting since curcumin is naturally derived from turmeric, which is one of the major ingredients of Asian cuisine [1, 23]. Of note, crude turmeric extracts have previously shown marked antibacterial activities against *S. aureus* [6, 65, 66]. This section discusses the synergistic antibacterial activity of curcumin with antibiotics against MSSA and MRSA. Table 2 summarizes studies that demonstrated the synergism of antibiotics-curcumin. In this table, we include the information of curcumin type, solvent, and concentration, type of bacteria-killing assay, and *S. aureus* strains for comparison.

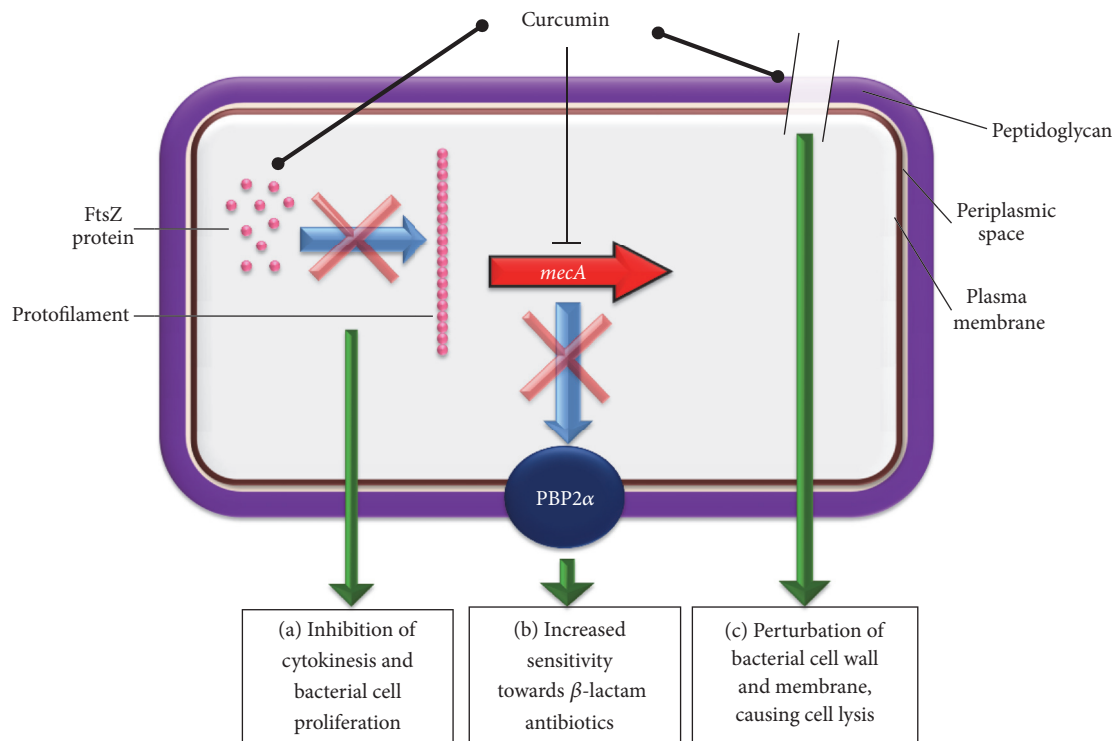


FIGURE 2: The potential mechanisms underlying the antibacterial effect of curcumin against *S. aureus*. Circle-shaped arrow indicates binding whereas blocked arrow represents inhibition. (a) Curcumin may bind into FtsZ proteins, thereby inhibiting the assembly of FtsZ protofilaments. This, in turn, suppresses the formation of Z-ring leading to inhibition of cytokinesis and bacterial proliferation [44]. (b) In the case of MRSA, curcumin could inhibit the *mecA* gene transcription, causing reduced expression of PBP2 α proteins. As a result, MRSA can be sensitized towards the antibacterial action of β -lactam antibiotics such as Penicillin and Methicillin [32]. (c) The binding between curcumin and peptidoglycan on *S. aureus* cell wall could trigger damage on the cell wall and membrane, leading to cell lysis of *S. aureus* [30, 32].

TABLE 2: Synergism of curcumin against *S. aureus*.

Compound (solvent)	Subinhibitory concentration	Antibiotics	<i>S. aureus</i> strain	Test method	Reference
Curcumin (not reported)	500 μ g/disc	Cefixime Cephotaxime Vancomycin Tetracycline	MSSA (1 clinical isolate)	Disk diffusion	[31]
Curcumin (DMSO)	Checkerboard (various serial dilutions)	Oxacillin Ampicillin Ciprofloxacin Norfloxacin	MSSA (ATCC 25923) MRSA (ATCC 33591) MRSA (1 clinical isolate)	Broth microdilution	[9]
Curcumin-1 (DMSO)	Checkerboard (various serial dilutions)	Cefaclor Cefodizime Cefotaxime	MSSA (MTCC 902)*	Broth microdilution	[41]
Curcumin (DMF)	25 μ g/mL	Gentamicin Amikacin Ciprofloxacin	MSSA (ATCC 25923) MRSA (ATCC 43300) MSSA (1 clinical isolate) MSSA (10 environ. isolates)	Disk diffusion & broth microdilution	[8]
Curcumin (DMSO)	32 μ g/mL	Penicillin Erythromycin Ciprofloxacin	MSSA (ATCC 25923) MSSA (13 clinical isolates)	Disk diffusion	[48]

* Purchased from Microbial Type Culture Collection Centre (MTCC), IMTECH, Chandigarh, India.

The first study that reported the synergism of curcumin against *S. aureus* was seven years ago by Moghaddam et al. [31]. Using a disk diffusion method, Moghaddam et al. [31] showed that 500 $\mu\text{g}/\text{disc}$ of curcumin exerted synergistic antibacterial effect on the MSSA when used in combination with four antibiotics. Combination with cefotaxime, cefixime, tetracycline, and vancomycin resulted in increase of inhibition zone of 52.6, 24.9, 26.5, and 24.4%, respectively. This was then followed by Mun et al. [9] study in 2013 that showed curcumin's synergism with Oxacillin, Ampicillin, Ciprofloxacin, and Norfloxacin against the MRSA. This study employed checkerboard broth microdilution assay method to determine the synergistic activity. This method allows more standardised testing and is less laborious and suitable for studies with multiple concentrations of test compounds [67]. Other studies also showed the synergistic antibacterial effect of curcumin against both MSSA and MRSA when used in combination with antibiotics such as Cefaclor, Cefodizime, Cefotaxime, Gentamicin, Amikacin, Penicillin, and Erythromycin (refer to Table 2). Based on reported findings, the curcumin synergism in combination with antibiotics appears to be relatively nonspecific. Antibiotics classes that have shown synergism with curcumin include β -lactams, Cephalosporins, Aminoglycosides, Glycopeptides, Tetracyclines, and Fluoroquinolones. This might be due to the multitargeting action of curcumin or their undetermined breakdown products as pointed out in the previous section. More studies are needed to evaluate the mechanism of curcumin synergism based on the different classes of antibiotics. In addition to antibacterial action, curcumin also reverses the drug resistance when used in combination with other anticancer agents such as cisplatin, 5-fluorouracil, oxaliplatin, and doxorubicin in multiple types of cancer cells including breast [68], colon [69], head and neck [70], and ovary [71]. The curcumin may have acted on the target or pathway related to the development of drug resistance, hence restoring the killing effect of the drugs [72, 73]. This may be one of the mechanisms on how curcumin enhances the effect of antibacterial drugs, especially when they are targeting *S. aureus*-infected human cells.

In recent years, MRSA infection has emerged as a serious infection due to its multidrug resistance (MDR) especially in the hospital setting [74]. The MRSA infection may spread rapidly especially when the disease is not well controlled. Curcumin exhibits potent activity against MRSA, not only when used alone, but also in combination with other antibiotics. In an effort to understand the curcumin's anti-MRSA effect, Mun et al. [32] showed that the Tris and Triton X-100 inhibited the bacterial growth to 63% and 59%, respectively, when used together with curcumin. This suggests that bacterial membrane permeability is partly responsible in regulating the antibacterial efficacy of curcumin against MRSA. The same group has also shown that ATPase inhibitors (DCCD and NaN_3) which block the ATP-binding cassette (ABC) enhanced the MRSA killing when used together with curcumin. The importance of membrane permeability/integrity in curcumin effect was also confirmed when the increase of peptidoglycan (PGN) concentration successively blocked the curcumin antibacterial activity [32]. These findings suggest that any drug or inhibitor that primarily acts on the bacterial

membrane has higher chance of showing enhanced activity when used together with curcumin. It is also noteworthy that the expression of Penicillin-binding protein 2 α (PBP2 α), a protein responsible in conferring resistance towards β -lactam antibiotics, was downregulated in MRSA upon curcumin treatment [32]. This protein which is encoded by *MecA*, a nonnative gene in MRSA has significantly reduced affinity for β -lactam antibiotics such as Methicillin and Penicillin. Cell-wall biosynthesis, the target of β -lactam, could therefore carry on in MRSA despite the presence of potent doses of these antibiotics [75]. The detailed mode of action of curcumin in inhibiting PBP2 α expression in MRSA is not clear at this juncture. It is plausible that curcumin may act on the transcription of *MecA* gene, thereby blocking the expression of PBP2 α protein (Figure 2).

In addition to antibiotics, there are evidences showing that curcumin augments the activity of other natural compounds against MSSA and MRSA. Balan et al. [76] demonstrated that combination of curcumin and whey proteins markedly inhibited *S. aureus* growth *in vitro*. Sharma et al. [77] have also previously reported the combination effect of curcumin with several phytochemicals such as cinnamaldehyde, ellagic acid, and eugenol against *Staphylococcus epidermidis* (*S. epidermidis*), which is closely related to *S. aureus*. The combination activities as such against *S. aureus* remain to be investigated. Indeed, there have been many studies showing the potent antibacterial action of other natural compounds against *S. aureus* such as thymoquinone [78], rhein [79], emodin [80], silibinin [81], osthol [82], tannic acid [83], and epigallocatechin gallate [84]. These findings warrant the potential use of abovementioned compounds in combination with curcumin against *S. aureus*.

4. The Challenges of Using Curcumin as Antibiotic

Cumulative findings suggest that curcumin has broad-spectrum antibacterial activities and has synergistic effects with other antibiotics in combination therapies *in vitro* [1, 6, 85]. Curcumin has also shown potent antibacterial action in the mouse model [40]. Nonetheless, the curcumin antibacterial activity has never been evaluated in clinical trials with an aim of using it as a future antibiotic. In this section, we discuss the underlying challenges from the clinical perspectives in developing curcumin into a potential antibiotic.

While curcumin is known to possess the pharmacological activities at relatively low doses, several studies have evidenced some cytotoxicity of curcumin [50–54, 86]. The first study that demonstrated the curcumin toxicity was by Goodpasture and Arrighi [50]. They showed that turmeric resulted in an induction of chromosome aberrations in tested cell lines starting from 10 $\mu\text{g}/\text{mL}$. Other studies have also shown the toxic effects of curcumin mainly on the DNA damage and chromosome aberrations [51–53]. While DNA alteration is the starting point of carcinogenesis, the use of curcumin under abovementioned conditions might be an issue. In other words, curcumin treatment may cause cancers even though the anticancer action of curcumin is well documented. In 1993, a study has concluded that turmeric oleoresin (turmeric

extract containing 79–85% of curcumin) has carcinogenic property in rats and mice [54]. Mice taking 0.2 mg/kg body weight of curcumin daily average were found to have carcinomas in their small intestines. Curcumin has also shown to promote lung cancer in another study [55]. The tumour-promoting activity of curcumin has been linked to the induction of reactive oxygen species (ROS) production such as superoxide anion and hydrogen peroxide [87–89].

As curcumin is an active iron chelator, it may potentially affect systemic iron metabolism especially those who have suboptimal iron status [56]. Furthermore, curcumin has been reported to block the enzymes that metabolize drugs such as cytochrome P450s [57, 58]. This may lead to the accumulation of nonmetabolized drugs in blood and result in undesired toxicity. In human, nonetheless, the side effects of curcumin have been relatively mild. A human trial has shown that curcumin ranging from 0.9 to 3.6 g per day up to 4 months only caused some adverse effects that included nausea, diarrhea, and increased serum alkaline phosphatase and lactate dehydrogenase [90]. In 2010, Balaji and Chempakam [91] have predicted a few toxigenic and potent compounds from turmeric using a cost-effective cheminformatics approach. This method can be adopted to select the effective but non-toxic curcumin or its derivatives for further biological studies. However, the selected compound has to be evaluated in a long-term study at its active dose against *S. aureus* in order to confirm the safety of using curcumin as a potential antibiotic.

Curcumin is usually extracted from turmeric plant mainly by solvent extraction followed by column-based purification [2, 3]. Curcumin is sparingly soluble in water (<0.1 mg/mL) and is mainly dissolved in organic solvents such as DMSO, DMF, or ethanol (Tables 1 and 2). This may be the major concern when it is administered into human system as human plasma is composed of 92% of water. The water-insoluble nature may affect curcumin bioavailability and hence affect its pharmacological potential [26, 27, 61]. To this end, several methods have been developed in recent years to circumvent the poor solubility and stability of curcumin, thereby maximizing its pharmacological or biological actions. For example, it has been reported that the use of heat could enhance the curcumin solubility [59, 60]. Kurien et al. [59] have reported the improved water solubility of curcumin from 0.6 to 7.4 $\mu\text{g}/\text{mL}$, without displaying heat-mediated destruction of the chemical structure. Development of curcumin bioconjugates has also shown to be an effective method of enhancing the curcumin solubility. For instances, conjugation of curcumin with hyaluronic acid formed micelles in aqueous phase at physiological pH and appeared to be non-toxic [92]. Dey and Sreenivasan have also conjugated curcumin with alginate, a natural polysaccharide product, in order to increase its stability and bioavailability [93]. Other macromolecules that could serve as carrier systems for curcumin include beta-casein [94], chitosan/Tween 20 [95], emulsomes [96], sodium caseinate [97], and albumin [98, 99]. The development of curcumin nanoformulations has been extensively reviewed in light of its anticancer action [100–102]. While increasing number of curcumin nanoformulation is being introduced into the therapeutic field, it is important to ensure that the bioconjugates or nanoformulations do not

TABLE 3: Challenges of curcumin use in clinical setting.

Challenge	References
<i>Cytotoxicity</i>	
DNA damage and chromosome aberrations	[50–53]
<i>Carcinogenesis</i>	
Promote tumour formation <i>in vivo</i>	[54, 55]
<i>Iron chelation</i>	
Alter systemic iron metabolism	[56]
<i>Enzyme inhibition</i>	
Inhibit drug-metabolizing enzymes	[57, 58]
<i>Solubility</i>	
Hydrophobic nature does not support water solubility	[59, 60]
<i>Bioavailability</i>	
Degradation by plasma protease and nonspecific protein binding	[26, 27, 61, 62]

diminish the antibacterial effects of curcumin at the expense of improved bioavailability in order to develop them into effective antibiotics in the future.

In addition to potential toxicity, poor solubility, and low bioavailability, curcumin encounters multiple challenges when it is administered either through oral or intravenous route due to the nature of body system [26, 59, 61, 62]. A large amount of curcumin may get degraded in the presence of detoxifying and metabolic enzymes, or it may bind to the circulatory proteins such as albumin which may potentially reduce its activity. Contradictorily, there have been evidences showing that degraded products from curcumin are responsible of its pharmacological activities [26, 27]. Furthermore, it has been shown that albumin-bound curcumin exerted similar level of activity compared to the DMSO-dissolved curcumin in serum [103]. Of note, the curcumin degradation and binding with physiological proteins have not been evaluated in light of the curcumin antibacterial action. Whether or not these factors would affect the activity of curcumin, further investigations are required. Notably, development of the curcumin bioconjugates, nanoformulations, or derivatives could be the key to overcome the challenges mentioned above (summarized in Table 3). The development of modified curcumin has been recently reviewed [62, 100, 101].

5. Conclusion

Curcumin has shown potent antibacterial activity and other pharmacological actions in the past 50 years. Curcumin has been marketed globally as a health supplement mainly for its antioxidant and anti-inflammatory properties. In addition, it also has high potential to be developed into an antibiotic against *S. aureus* and other bacterial strains in the future. However, the challenges mentioned in the preceding sections should be taken into consideration to open the door for the development of more biologically active curcumin derivatives. To the best of our understanding, this is the first review that compares and summarizes the curcumin antibacterial

activity against *S. aureus*. More investigation is required in order to better understand the broad action of curcumin prior to develop this compound or its derivatives into a potential antibiotic.

Competing Interests

The authors declared that there are no competing interests.

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