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Review

Impact of curcumin nanoformulation on its antimicrobial activity

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ABSTRACT

Background: Curcumin is a yellow-orange, hydrophobic compound extracted from *Curcuma longa* and widely used by oriental cultures. It displays numerous biological activities and shows antimicrobial activity against both Gram-positive and Gram-negative bacteria, as well as yeasts and molds. However, its low water solubility decreases its bioavailability and hinders its industrial use. Curcumin may be modified by micro/nanoencapsulation or nanonization (transformation in nanometric crystals) techniques, to improve its water solubility and dispersibility and potentiate its biological properties. Furthermore, encapsulated curcumin may be applied to foods as a preservative, to increase the product's shelf life.

Scope and approach: In this work, the recent developments in the antimicrobial activity of micro- and nanoformulations (nano/microparticles, capsules and nanocrystals) of curcumin are comprehensively reviewed. Also, the most common methods applied for antimicrobial determination are listed and discussed, highlighting the conflicting results of inhibitory concentration that may be found by each technique.

Key findings and conclusions: When evaluating the antimicrobial properties of curcumin, it becomes important to determine the actual gains from encapsulation because these techniques are usually expensive and may lead to the degradation of curcumin during the encapsulation steps. Attention must be paid when choosing the most suitable experimental method to determine the antimicrobial activity of encapsulated curcumin because minimum inhibitory concentration values may vary significantly.

1. Introduction

Curcumin is the main product from extraction of *Curcuma longa* rhizome, being widely used by Asian pharmacology and medicine (particularly in China and India), due to its various biological activities and intrinsic low toxicity (Deshpande et al., 1998; Kumavat et al., 2013; Qureshi, Shah, & Ageel, 1992; Shlar et al., 2015). Commercial extracts typically contain a mixture of curcuminoid derivatives, and typical values are 5.69–2.86% curcumin, 1.47% demethoxycurcumin and 1.36% bisdemethoxycurcumin (Li, Yuan, Deng, Wang, & Yang, 2011) (Fig. 1). Studies of curcumin have demonstrated diverse biological properties, such as antiproliferative (Dubey, Sharma, Narain, Misra, & Pati, 2008) and chemopreventive (Duvoix et al., 2005) effects, cytotoxicity to certain cell lines (Lal, Gupta, Thavaselvam, & Agarwal, 2013), anti-inflammatory (Rocha et al., 2014), antioxidant (Carvalho, Takeuchi, Geraldine, Moura, Célia, et al., 2015), antimutagenic (Fernández-Bedmar & Alonso-Moraga, 2016), anti-amyloid (Mathew et al., 2012), wound healing (Krausz et al., 2015), neuroprotective (Mythri & Bharath, 2012), biofilm formation inhibition (Hu, Huang, & Chen, 2013) and antimicrobial activity (suitable references are given later).

However, the practical applications of curcumin are often limited by its low water solubility and sensitivity to alkaline conditions, heat, light, metal ions, enzymes, oxygen and ascorbic acid, among others (Paradkar, Ambike, Jadhav, & Mahadik, 2004; Paramera, Konteles, & Karathanos, 2011). In this sense, curcumin is a promising candidate for the development of new natural materials, such as micro/nanoparticles and nanocrystals, to enhance its stability against aforementioned factors and harness biological properties (Shlar et al., 2015; Wang, Tan, Zhong, Chen, & Wang, 2011).

The antimicrobial property of curcumin is well-known and the mechanism involves the interaction with the essential cell division initiating protein FtsZ. The bacterial cytoskeleton is necessary for growth and cellular division, while the FtsZ protein is involved in bacterial cell

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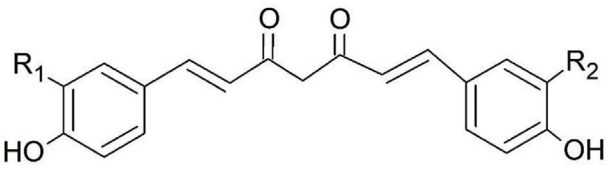

Fig. 1. Chemical structure of curcuminoids.
Curcumin: R_1 = OCH_3; R_2 = OCH_3
Demethoxycurcumin: R_1 = OCH3; R_2 = H
Bisdemethoxycurcumin: R_1 = H; R_2 = H.

division and is the first protein to appear at the impending site of division. FtsZ is present in almost all prokaryotic species and is also essential for the division of chloroplasts and mitochondria in some eukaryotes. Immunolocalization experiments showed that in the bacteria, the FtsZ protein undergoes polymerization, forming a ring structure known as the Z-ring, at the imminent division site. The ring structure indicates that FtsZ is a cytoskeletal protein, exhibiting functional homology with tubulin, a eukaryotic cytoskeleton protein. However, the structures of bacterial cytoskeleton proteins are markedly different from their eukaryotic homologs, making it possible to develop specific inhibitors for bacterial proteins (Kaur, Modi, Panda, & Roy, 2010; Rai, Singh, Roy, & Panda, 2008). A comprehensive illustration of the molecular docking of curcumin is found in Kaur et al. (2010).

Experimental data support that the methoxy and hydroxyl groups of curcumin are directly involved in the antimicrobial activity (Fujikawa et al., 1969; Gotoh, Saitoh, & Miyake, 1998; Han & Yang, 2005; Tesaki et al., 1998). Using molecular docking, Kaur et al. (2010) demonstrated that the oxygen molecules of phenol, methoxy functional groups (linked to phenolic rings) and two carbonyl groups of curcumin interact the catalytic site of FtsZ by forming hydrogen bonds and, potentially, non-specific, hydrophobic interactions. Therefore, these functional groups have important roles in the interaction between curcumin and FtsZ. In one study, curcumin strongly inhibited the formation of the cytokinetic Z-ring in *Bacillus subtilis* 168 without affecting the segregation and organization of the molecule. The authors of this study concluded that curcumin hinders bacterial cell division by preventing the assembly dynamics of FtsZ in the Z-ring (Rai et al., 2008).

2. *In vitro* antimicrobial susceptibility testing

Numerous laboratory methods are available to measure the *in vitro* susceptibility of bacteria to antimicrobial agents, and these may be divided into two main categories: diffusion methods and dilution methods. The correct choice of the antimicrobial susceptibility test methods is of fundamental importance when evaluating nano/microparticles, due to the possibility of sedimentation or the occurrence of turbidity, leading to incorrect conclusions.

Diffusion methods are performed by inoculating Mueller-Hinton agar plates with the test microorganism and then applying the antimicrobial agent on the inoculated agar surface. If paper disks are used, this method may be called disk diffusion. Alternatively, it is called well diffusion, when the antibiotic is placed in small wells containing the agar (Silveira, Olea, Mesquita, Cruz, & Mendes, 2009). The plates are then incubated at 35 °C for 16–24 h, before determination of the results. Zones of growth inhibition around each of the antibiotic disks/wells are measured to the nearest millimeter (Clinical and Laboratory Standards Institute [CLSI], 2015a; Jorgensen & Ferraro, 2009).

Variations of the diffusion methods are also used. The antimicrobial gradient method (Etest) is a diffusion method in which a strip impregnated with an increasing concentration gradient of the antimicrobial agent across its length is deposited on an agar medium, previously inoculated with the microorganism of interest. The well diffusion method is suitable to evaluate the antimicrobial activity of plants or microbial extracts (Magaldi et al., 2004; Valgas, Souza, Smânia, & Jr, 2007). The agar plug diffusion method is often used to highlight the antagonism between microorganisms (Elleuch et al., 2010). The cross streak method can rapidly screen microorganisms for antagonism (Lertcanawanichakul & Sawangnop, 2008). The poisoned food method is often used to assess the antifungal effect against molds (Balouiri, Sadiki, & Ibnsouda, 2016).

Dilution methods involve preparing two-fold dilutions of the antimicrobial agent in a liquid growth medium dispensed in test tubes. The antimicrobial-containing tubes are inoculated with a standardized bacterial suspension (1–5 × 10^5 colony-forming units [CFU]/mL). The tubes can be examined for visible bacterial growth, as evidenced by turbidity after overnight incubation at 35 °C (CLSI, 2015b; Jorgensen & Ferraro, 2009). Agar dilution methods can also be used. In this approach, the bacteria are inoculated onto the surface of the agar, containing different concentrations (two-fold dilutions) of the antimicrobial agent.

Other notable methods include the time-kill test (or time-kill curve), being the most appropriate method for determining the bactericidal or fungicidal effect. It is a strong tool for obtaining information about the dynamic interaction between the antimicrobial agent and the microbial strain because it reveals a time-dependent or a concentration-dependent antimicrobial effect (Pfaller, Sheehan, & Rex, 2004).

Each method has its advantages and limitations, including the organisms that may be accurately tested. Dilution methods provide quantitative results, such as the minimum inhibitory concentration (MIC), which is defined as the lowest concentration of antimicrobial agent required to inhibit the bacterial growth.

The CLSI publishes standardized procedures for both antimicrobial disk and dilution procedures including the type of culture medium, incubation temperature and time, and inoculum concentration (Table 1). All *in vitro* antimicrobial testing techniques were recently reviewed in detail by Balouiri et al. (2016) and are beyond the scope of this review. Antimicrobial activity parameters are reproduced below, given their importance in understanding the results obtained by nanoencapsulated curcumin.

3. Antimicrobial activity of curcumin: free (non-encapsulated) form

Although the biological activity of curcumin in nano formulations (nanoencapsulated or with nanometric size) was discussed elsewhere (Flora, Gupta, & Tiwari, 2013; Hussain, Thu, Ng, Khan, & Katas, 2017; Silva et al., 2016), the impact of encapsulation on antimicrobial activity is a hot topic (Hussain, Thu, Amjad, et al., 2017).

Antimicrobial activity was also reviewed in the literature (Moghadamtousi et al., 2014). Antimicrobial properties of free form curcumin have been reported against a broad range of microorganisms, including the Gram-positive bacteria *B. cereus, Bacillus subtilis, Staphylococcus aureus, Streptococcus mutans, Staphylococcus epidermidis* and Gram-negative *Escherichia coli, Pseudomonas aeruginosa, Yersinia enterocolitica* and *Shigella dysenteriae* (Bhawana, Basniwal, Buttar, Jain, & Jain, 2011; Dubey et al., 2008; Han & Yang, 2005; Hu et al., 2013; Liu & Huang, 2012; Luo & Yang, 2014; Mun et al., 2013; Parvathy, Negi, & Srinivas, 2009; Rahayu, Nurdiana, & Santoso, 2013; Rai et al., 2008). It was demonstrated that the curcuminoids extraction step critically influences the antimicrobial properties of the extracts (against foodborne pathogen—a coliform group of bacteria, fecal coliform, *Salmonella*, and total fungal counts), (Gul & Bakht, 2015).

Demethoxycurcumin also presents antimicrobial activity, as demonstrated by Luo and Yang (2014), using broth microdilution and microcalorimetric studies and dimethyl sulfoxide (DMSO) as the solvent. The MICs of demethoxycurcumin were 512, 1024, and 1024 μg/mL for *E. coli, S. aureus*, and *S. dysenteriae*, respectively. This result is valuable, considering that commercially available curcumin (powder or oleoresins) is a mixture of curcumin derivatives. Singh and Jain (2012) separated the components of turmeric extract by column

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