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Cytotoxicity and Antibacterial Effect of Trp-Substituted CM11 Cationic Peptide Against Drug-Resistant Isolates of *Brucella melitensis* Alone and in Combination with Recommended Antibiotics

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Abstract
During the recent years, antibiotic resistance of pathogenic bacteria to conventional and common antibiotics has considered as a global concern. Therefore, researchers attend to find a new class of antimicrobial agents such as antimicrobial peptides (AMP), but some limitations are on the therapeutic use of AMPs such as cytotoxicity. To overcome these limitations various strategies have been described such as designing AMP analogues and/or combined use of them with synergistic effects. According to the many studies substitution of tryptophan as an amino acid residue with negative hydropathy index (−0.9) to the leucine residue that is an amino acid with high positive hydropathy index (3.8) can enhance bactericidal activity and reduce cytotoxicity. Based on this topic in this study, a peptide modification was done by substitution of tryptophan at position 3 (leucine amino acid) of the CM11 antimicrobial peptide to promote its antibacterial activity and decrease cytotoxicity effect on eukaryotic cells. In the following, we investigated peptide antibacterial activity alone and in combination with common antibiotics against drug-resistant isolates of *Brucella melitensis*. Specific antibiotics were selected considering the CLSI guideline and peptide-antibiotics synergistic effect was done by checkerboard procedure through the broth microdilution method. In comparison with the CM11 peptide, modified peptide exhibited similar antimicrobial activity against clinical isolates of antibiotic-resistant *B. melitensis* with a reduction in hemolytic and cytotoxicity activates. Also, the synergistic effect between modified peptide and streptomycin and rifampin was observed as synergy and additive, respectively.

Keywords *Brucella melitensis* · Antibiotic resistance · Antimicrobial peptide · Synergistic effect · Amino acid substitution

Introduction

Brucellosis is a contagious disease of animals caused by species of the genus *Brucella* that their classification is mainly based on the difference in pathogenicity and in host preference (Cardoso et al. 2006). In human brucellosis is usually caused by *Brucella melitensis* as a major debilitating disease with worldwide distribution (Mohammadi Azad et al. 2017). The disease prevalence is much higher in developing as compared to developed countries so far is still common in the Middle East, Asia, Africa, South and Central America, the Mediterranean basin and the Caribbean. Zoonotic transmission of *Brucella* to human may occur via ingestion the contaminated food products, direct contact with an infected animal or inhalation of aerosols, while the person-to-person spread of brucellosis is extremely rare (Pappas et al. 2006; Piranfar et al. 2015). *Brucella* species are facultative intracellular parasites that can survive and replicate within professional and non-professional phagocytes. Generally, *Brucella* species penetrate the mucosa of the oral, nasal, or pharyngeal cavities and are phagocytized by host macrophage cells, where survival and replication occur (Guerra 2007; Silva 2012). It is noteworthy that the opsonized and non-opsonized *Brucella* bacteria are phagocytosed by the host macrophages but bacteria cells that opsonization by humoral factors such as complement or antibody are killed while the non-opsonized survive and replicate inside the phagocytic cells (Eze et al. 2000).

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