

Trichogin GA IV and Its Analogues: Mode of Action and Antibiotic Activity against Gram-Positive and MRSA Strains

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Introduction

Since their discovery during the 20th century, antibiotics have substantially reduced the threat posed by infectious diseases that were previously untreatable and fatal. These gains are now seriously jeopardized by the emergence and spread of microbes that are resistant to these drugs. One possible solution to this problem is offered by natural antimicrobial peptides (AMPs). These short peptides (about 10-20 aminoacids long, often exhibiting an amphipathic helical structure) are produced by virtually all organisms as a first line of defense against pathogens. In contrast to traditional antibiotic drugs, these molecules act simply by perturbing the bacterial membrane, making it permeable, and thus leading to cell death. For this reason they constitute excellent candidates for development as novel therapeutic agents. One of the main issues which has limited the widespread clinical application of AMPs is their susceptibility to proteolytic degradation. In this respect, the class of peptaibiotics could be particularly interesting. These natural peptides, produced by fungi, contain several non-coded residues, such as Aib (α -aminoisobutyric acid), which could confer resistance to proteolysis. In this study, we investigated the antibacterial, antifungal and hemolytic activities of the peptaibiotic trichogin GA IV, and of several synthetic analogues, as well as their susceptibilities to proteolytic degradation.

Results and Discussion

Trichogin GA IV is a member of a sub-class of peptaibols that are linear peptide antibiotics of fungal origin, characterized by the presence of a variable number of α -aminoisobutyric acid residues, an acyl group at the N-terminus and a 1,2-amino alcohol at the C-terminus. Several analogues of trichogin GA IV with amino acid substitutions or deletions were designed which allowed determination of the minimal inhibition concentrations against Gram-positive, Gram-negative and various pathogenic fungal cells (Table 1). In particular, trichogin GA IV and its analogues caused a dramatic increase in antibiotic activity against Gram-positive and methicillin resistance *Staphylococcus aureus* (MRSA) with low hemolytic effect. Our results suggest that trichogin GA IV and its analogues may be useful for the design of novel antibiotic peptides that possess high bacterial cell selective effects (as conventional antibiotic agents) but lack hemolytic activity and are not susceptible to enzyme digestion (Fig. 1).

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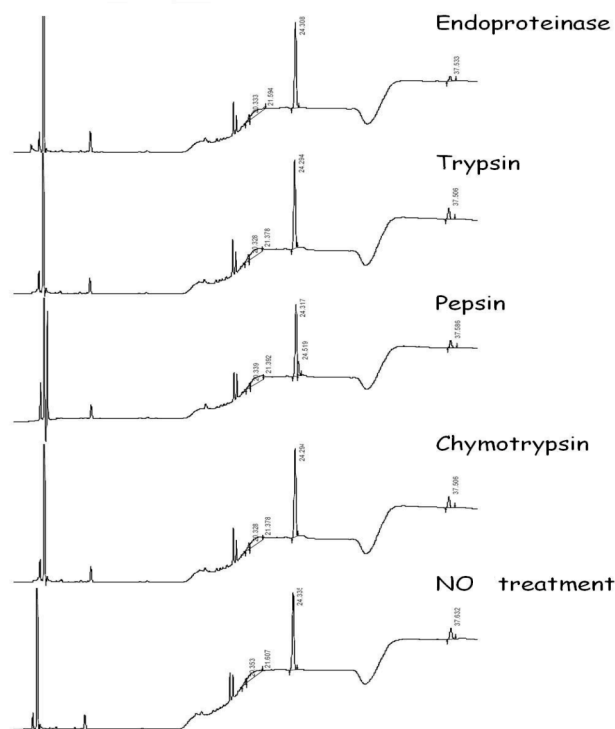


Table 1. Antibacterial activity against various pathogenic bacterial strains

Minimal inhibitory concentrations ($\mu\text{g}/\text{mL}$) for different bacteria						
	<i>S. aureus</i>	<i>S. epidermis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>B. subtilis</i>	<i>L. monocytogenes</i>
Trichogin GA IV	8~16	>32	32	>32	>32	32
Tric-OMe	16	>32	32	>32	>32	>32
Tric-TOAC	16~32	>32	>32	>32	>32	>32
Tric-8	>32	>32	>32	>32	>32	>32
Tric-4	>32	>32	>32	>32	>32	>32

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