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In vitro bactericidal activity of Lactoferricin and other enzymes on bacteria selected from dogs with pyoderma

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Lactoferricin (LFcin) is a peptide with antimicrobial activity against microorganisms such as Gram negative and positive bacteria, including some antibiotic-resistant pathogens. Others enzymes like dextrozyme, alcalase and amylase may be associated to the LFcin to enhance its antimicrobial action. The aim of this study was to evaluate the *in vitro* activity of LFcin associations with dextrozyme (LFD), alkalase (LFL) and amylase (LFM) against Staphylococcus pseudintermedius, Escherichia coli, Proteus vulgaris and *Pseudomonas aeruginosa* strains isolated from dogs with pyoderma. The evaluation was performed using minimum inhibitory concentrations with a microtiter plate dilution method starting by an LFcin/enzymes solution at 11%. The bacterial inoculums in log-phase growth were prepared in brain heart infusion broth (BHI) with a turbidity of 0.5 McFarland, corresponding to 102 to 103 cells/ml. Dilutions in BHI at 2:1 (7.5%), 1:1 (5.5%), 1:2 (3.7%) and 1:5 (1.8%) were used for each bacteria. Negative and positive controls were included. All the wells were incubated 10 µl on blood agar at 37° C for 48 hours to confirm the bacterial inhibition. The associations LFD and LFM showed bactericidal activity against all the isolates at 7.3%, at 5.5%, only for S. pseudintermedius at 3.7%. The LFL showed inhibition at 3.7% for all strains and resistance at 1.8%. These results suggest that the associations of LFcin with other enzymes improve its antimicrobial activity. The LFL exhibits *in vitro* bactericidal activity even against a strain of multidrug resistant P. aeruginosa at low concentrations. LFcin and its associations should be a new topical treatment of skin infections.

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Anti-resistance agent discovery targeting efflux pumps of multi-drug resistant pathogens using synthetic combinatorial libraries

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Antibiotic resistance is a major global health issue for the 21st century due to an increasing number of bacterial species has become multi-drug resistance. Many species have become resistant to the majority or all of antibiotics available and extremely toxic drugs are being used to cure these infections because there is nothing left to treat them. The increase of antibiotic resistance combined with the decrease of FDA approval for novel therapeutics is driving us rapidly towards a post antibiotic era where antibiotics will be obsolete. If this lack of novel therapeutics continues, resistant antibiotic infections will be the leading cause of death by the year 2050. Mixture based synthetic combinatorial library screening offers a tremendous enhancement for the rate of drug discovery. This is due to the fact that the activity of millions of compounds can be accessed through the testing of exponentially fewer samples. To this end, we utilized the synthetic combinatorial screening to identify anti-resistance agents that cause multi-drug resistant species to be once again susceptible to clinical antibiotics that are no longer effective. From the initial screening we selected a triamine peptide library that decreased the effective concentration of tetracycline towards a clinical multi-drug resistant *Pseudomonas aeruginosa* by 4-fold without displaying any inhibitory effects alone. Deconvolution of this library was performed using the positional scanning approach to identify the functional groups at each variant position that created the greatest decrease in the effective concentration of tetracycline. Triamine lead agents were shown to decrease the tetracycline 90% effective concentration by an average 7.4-fold. In addition, these compounds displayed efflux inhibition of ethidium bromide of Gram negative and Gram positive organisms. The lead agents were not effective towards bacterial mutant strains lacking a major efflux pump revealing specificity towards efflux inhibition. These results demonstrate that employing synthetic combinatorial libraries to screen for anti-resistance agents can create a fundamental shift away from the traditional screening processes by introducing a rapid approach to discover novel agents that create susceptibility in multi-drug resistant species.

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