Characterization of Antimicrobials From the Soil Bacterium Xenorhabdus szentirmaii

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Antimicrobial resistance(AMR) is a global health threat and the discovery of new antimicrobial compounds has been limited in the past four decades. New antimicrobials with new functions are urgently needed to address this pressing global issue. A potential new antimicrobial source is the soil bacteria Xenorhabdus spp., a symbiont of nematodes that invade the insect larvae. The nematodes regurgitate the bacteria, killing insect larvae by releasing toxins and antimicrobials and allowing the nematodes to extract nutrients. From cell-free cultures of Xenorhabdus szentirmaii, we established a novel protocol to separate unexplored antimicrobials into two distinct soluble forms: methanol and dimethyl sulfoxide (DMSO). Both forms can inhibit dangerous AMR bacteria, including methicillin resistant Staphylococcus aureus (MRSA). Further separation of methanol-soluble antimicrobials by high-performance-liquid-chromatography followed by mass spectrometry revealed new antimicrobial compounds including novel isoforms of fabclavine (peptide-polyketide antibiotic). Nuclear magnetic resonance and mass spectrometry revealed that the DMSO-soluble antimicrobials were novel lipopeptide-type antimicrobials with multiple isoforms. The antimicrobials of Xenorhabdus species are primarily produced by non-ribosomal peptide synthetases (NRPS) and polyketide synthetase (PKS) genes. Our global genome analysis revealed that X. szentirmaii contains 15 NRPS gene clusters and one hybrid NRPS-PKS gene. Mutation of the putative fabclavine biosynthetic gene encoded by the hybrid NRPS-PKS gene showed a reduced ability to inhibit both bacterial and fungal growth. In summary, our results substantiate the potential of Xenorhabdus szentirmaii as a promising natural source for future antimicrobial discoveries.