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Author(s)	Haedar, Jabal Rahmat
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Abstract of Doctoral Dissertation

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Title of Doctoral Dissertation

Studies on Natural Products from Untapped Bacterial Resources

(未開拓細菌類を起源とする天然物に関する研究)

Natural product (NP) and its derivatives have made a major contribution to drug discovery and development. Thousands of NPs have been clinically approved to treat various human diseases. However, new therapeutic agents are still required to treat cancer and infectious diseases. In addition, recent exploration of novel NPs is challenged by high-rate rediscovery of previously reported molecules. On the other hand, metagenomic analysis of many marine invertebrates and soil ecosystems revealed enormous of biosynthetic gene clusters (BGCs) encoded for new bioactive small molecules. Furthermore, these potential BGCs are associated with diverse and rare bacteria that have never been investigated before. Thus, targeting these untapped microbial strains from marine and soil ecosystems would lead to discovery of novel natural products.

This study covered explorations of novel NPs from untapped and rare bacterial strains living in marine invertebrates and soil ecosystem. In the first study, targeting promising yet uncultured symbiotic bacteria *Ca. Entotheonella* spp. living in marine sponge *Theonella swinhoei* allowed identification of three novel members of theonellapeptolides along with several known compounds. The molecular structures of the isolated compounds were elucidated by combination of NMR, tandem mass, and application of Marfey's method. All the identified NPs inhibited grow of pancreatic cancer cell line MIA PaCa2 in nutrition starvation condition. Among them, known theonellapeptolide member having combinations of amino acid residues of methyl β -alanine and methyl isoleucine at position 4 and 6 displayed the most potent activity, suggesting new potential biological activity for marine derived peptide compounds.

In the second study, we applied in situ cultivation approach to domesticate promising bacterial strains from soil ecosystems. Screening of ichip-bacterial strain collections based on antibacterial and iron chelating activities allowed detections of two rare bacteria, *Variovorax* sp. H002 and *Variovorax* sp. B014. Investigation of their metabolite profiles guided us to isolate and characterize eight novel and two known compounds. Their molecular structures were established by 2D NMR and tandem mass analyses followed by application of Marfey's method. In addition, their putative biosynthetic gene clusters were proposed by whole genome sequencing analysis. The isolated compounds showed strong ferric ion chelating activity as well as moderate antibacterial activity against gram-negative bacteria.

Finally, our findings demonstrated that untapped and rare bacteria living at marine and terrestrial are promising biologically active small molecules that can be developed as drug candidates.