Abstract

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Hepatitis C Virus NS3 Protease and Helicase Inhibitors from Red Sea Sponge (Amphimedon) Species in Green Synthesized Silver Nanoparticles Assisted by in Silico Modeling and Metabolic Profiling

Background: Hepatitis C virus (HCV) infection is a major cause of hepatic diseases all over the world. This necessitates the need to discover novel anti-HCV drugs to overcome emerging drug resistance and liver complications. Purpose: Total extract and petroleum ether fraction of the marine sponge (Amphimedon spp.) were used for silver nanoparticle (SNP) synthesis to explore their HCV NS3 helicase- and protease-inhibitory potential. Methods: Characterization of the prepared SNPs was carried out with ultraviolet-visible spectroscopy, transmission electron microscopy, and Fourier-transform infrared spectroscopy. The metabolomic profile of different Amphimedon fractions was assessed using liquid chromatography coupled with high-resolution mass spectrometry. Fourteen known compounds were isolated and their HCV helicase and protease activities assessed using in silico modeling of their interaction with both HCV protease and helicase enzymes to reveal their anti-HCV mechanism of action. In vitro anti-HCV activity against HCV NS3 helicase and protease was then conducted to validate the computation results and compared to that of the SNPs. Results: Transmission electron–microscopy analysis of NPs prepared from Amphimedon total extract and petroleum ether revealed particle sizes of 8.22–14.30 nm and 8.22–9.97 nm, and absorption bands at ?max of 450 and 415 nm, respectively. Metabolomic profiling revealed the richness of Amphimedon spp. with different phytochemical classes. Bioassay-guided isolation resulted in the isolation of 14 known compounds with anti-HCV activity, initially revealed by docking studies. In vitro anti–HCV NS3 helicase and protease assays of both isolated compounds and NPs further confirmed the computational results. Conclusion: Our findings indicate that Amphimedon, total extract, petroleum ether fraction, and derived NPs are promising biosources for providing anti-HCV drug candidates, with nakinadine B and 3,4-dihydro-6-hydroxymanzamine A the most potent anti-HCV agents, possessing good oral bioavailability and penetration power.