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Optimization of PhysicoChemical Parameters for Production of Cytotoxic Secondary Metabolites and Apoptosis Induction Activities in the Culture Extract of a Marine Algal–Derived Endophytic Fungus *Aspergillus* sp.

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The endophytic fungal community in the marine ecosystem has been demonstrated to be relevant source of novel and pharmacologically active secondary metabolites. The current study focused on the evaluation of cytotoxic and apoptosis induction potential in the culture extracts of endophytic fungi associated with *Sargassum muticum*, a marine brown alga. The cytotoxicity of the four marine endophytes, *Aspergillus* sp., *Nigrospora sphaerica*, *Talaromyces purpureogenus*, and *Talaromyces stipitatus*, was evaluated by the MTT assay on HeLa cells. Further, several physicochemical parameters, including growth curve, culture media, and organic solvents, were optimized for enhanced cytotoxic activity of the selected extract. The *Aspergillus* sp. ethyl acetate extract (ASE) showed maximum cytotoxicity on multiple cancer cell lines. Chemical investigation of the metabolites by gas chromatography–mass spectroscopy (GC-MS) showed the presence of several compounds, including quinoline, indole, 2,4-bis(1,1-dimethylethyl) phenol, and hexadecenoic acid, known to be cytotoxic in ASE. The ASE was then tested for cytotoxicity *in vitro* on a panel of six human cancer cell lines, namely, HeLa (cervical adenocarcinoma), MCF-7 (breast adenocarcinoma), Hep G2 (hepatocellular carcinoma), A-549 (lung carcinoma), A-431 (skin/epidermis carcinoma), and LN-229 (glioblastoma). HeLa cells were most vulnerable to ASE treatment with an IC_{50} value of 24 ± 2 μg/ml. The mechanism of cytotoxicity exhibited by the ASE was further investigated on Hela cells. The results showed that the ASE was capable of inducing apoptosis in HeLa cells through production of reactive oxygen species, depolarization of mitochondrial membrane, and activation of the caspase-3 pathway, which shows a possible activation of the intrinsic apoptosis pathway. It also arrested the HeLa cells at the G2/M phase of the cell cycle, eventually leading to apoptosis. Through this study, we add to the knowledge about the marine algae associated with fungal endophytes and report its potential for purifying specific compounds responsible for cytotoxicity.

Keywords: marine macroalga, *Sargassum muticum*, endophytic fungi, *Aspergillus* sp., cytotoxic compounds, apoptosis 3