Abstract

In my thesis, the primary objective was to identify the NP-based anticancer lead molecules for drug discovery. Work was focused on LCMS-based dereplicationm metabolomics and network pharmacological approaches. *A. cunninghamii* Mudie plant was selected for the thisis work. Stretgy one was focused on the dereplication to target the new metabolites from the A. *cunninghamii* Mudie: gum-resins. And second strategy was focused to LCMS-based metabolomis and network pharmacology to understand the cytotoxic mechanism of secondary metabolites of *A. cunninghamii Mudie*: leaves. In the gum resin of *A. cunninghamii* Mudie, a new molecule agatheol methylether and eight known labdane diterpenoid and five abietane diterpenoids were isolated. All these compounds were characterized by 1D and 2D NMR (^{1}H, ^{13}C- DEPT-135, ^{1}H-^{1}H COSY, HSQC, and HMBC experiments) and HRMS analysis. Thereafter, cytotoxicity activity of compounds has been screened against human cancer cell lines (A549, SCC09, MDAMB231, HS578T, FaDU, Molt4, and MCF7) and breast epithelial *cell line(fr2) as well* by employing MTT assay. Compound agatheol methylether seemed to be most active with IC_{50} values of 9 μg/mL against Hs 578T and MOLT-4 cells, showing that it can be a potential anticancer lead molecule. Molecular docking interaction of active compounds with anticancer target *α, β*-tubulin (PDB ID: 1JFF) and EGFR (PDB ID: 6DUK) has been performed. The binding energy of compounds ranged from -6.06 kcal mol^{-1} to -7.22 kcal mol^{-1} against *α, β*-tubulin dimer protein, and from -8.8 Kcal mol^{-1} to -7.11 Kcal mol^{-1} against EGFR protein, respectively. The binding energy, ligand efficiency, and interactions of ligands with *α, β*-tubulin protein (PDF: 1JFF) and EGFR (PDB ID: 6DUK) are evaluated respectively. In the leaves of *A. cunninghamii* Mudie, the extract exhibited significant cytotoxic potential, with an IC50 value of 25 μg/mL. The extract was planned for phytochemical investigation for the isolation of bioactive secondary metabolites via bioassay-guided fractionation, combined with LC-HRMS analysis and DNP strategic database mining. Further, eight (AC1-AC8) compounds were characterized by using 1D and 2D NMR (^{1}H, - ^{13}C,

Abstract

DEPT-135, ^{1}H-^{1}H COSY, HSQC, and HMBC experiments) spectrum and HRMS. Additionally, Compounds were evaluated for *in-vitro* cytotoxicity studies against human gastric adenocarcinoma (AGS cell line), *in-silico*, eight compounds (AC1-AC8) were selected for network pharmacology analysis and AC8 was rejected based on Lipinski's rule violations in the virtual ADME analysis. Molecular docking studies of compounds with EGFR, PIK3R1 AND GSK3B were evaluated with minimum binding affinity -7 kcal/mol to -9.4 kcal/mol. Molecular simulations of compound AC2 and AC5 against GSK3β and EGFR shows avg RMSD deviation were found 0.55-0.66 nm at around 25ns. All these results suggest that the ligand was finding its most favourable binding state as the simulation run progressed, all these results suggest that at the initial stage, the ligand was finding its most favourable binding state as the simulation run progressed, the ligand was found quite stabilized in the binding pocket.

In future these secondary metabolites may be used for drug discovery, detailed pharmacological and toxicological studies may be planned on the identified lead