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Structure-guided cancer blockade between bioactive bursehernin and proteins: Molecular docking and molecular dynamics study

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ABSTRACT

Bursehernin (5′-desmethoxyyatein) is a natural lignan, which has anti-tumor activity *in vitro*. In this study, the binding-inhibitory effects of bursehernin were screening on selected 80 proteins associated with cancer pathway. The computational analysis suggested inhibitory effect due to bursehernin towards proteins related to cancer proliferation, including FMS kinase receptor, heat shock protein 90-α (Hsp90-α), adenylate cyclase 10 (ADCY10), mitogen-activated protein kinase kinase (MEK1), and α-tubulin. Moreover, bursehernin could interfere with cell cycle progression via binding to cyclin B proteins. Among all screened proteins, the compound showed an interesting binding affinity to the FMS kinase receptor. The binding mode studies by molecular dynamic technique showed that aromatic ring of bursehernin compound was responsible for compound-protein interaction through pi-pi stacking with Tyr105 and Phe178 of the FMS kinase receptor. This study suggests that bursehernin has potential for development as an anti-tumor agent with an anti-proliferation, and cell cycle arrest inducing, although further studies are needed.

1. Introduction

Cancer is a malignant neoplasm caused by abnormal and uncontrolled cell proliferation, and becomes to the major cause of death worldwide. In cancer cells, proliferative signals regulation is compromised leading to increased growth factor production, stimulating normal cells in the microenvironment to provide cancer cells with growth factors, increasing the number of receptors on the cell surface, structurally altering receptors to facilitate cancer cell signaling and activating proteins in the downstream signaling pathway [1]. The cell cycle is a highly conserved and tightly regulated biological system that controls cellular proliferation and differentiation. Alterations in cell cycle regulatory proteins such as cyclin and cyclin dependent kinases (CDKs), leading to the loss of normal cell-cycle control, are a hallmark of many cancers [2]. Many proteins play an important task in regulating tumor cell proliferation and differentiation, including FMS kinase receptor, Hsp90-α, ADCY10, MEK1 and α-tubulin proteins. Overexpression of the colony stimulating factor-1 receptor (CSF-1R), also known as M-CSFR or FMS receptor, associated with the growth of several tumor types including leukemia, breast, prostate and ovarian cancer [3–6].

The FDA-approved anti-cancer drugs are normally specific to one of protein targets in cancer cells, for example, Vincristine-β-tubulin, Vinblastine-mitotic spindle, Tamoxifen citrate-estrogen receptor (ER), Etoposide-DNA topoisomerase II, Trastuzumab-HER-2, Erlotinib and Panitumumab-EGFR and Tofacitinib-JAK2 proteins [7]. Chemotherapy and specifically targeted drugs have been developed to disrupt the target, thereby inducing cell death and impeding progression of malignant changes in cells. In general, treatment of cancer is difficult because of the side effect of the chemotherapeutic drugs on the normal cells. Therefore, developing the new therapeutic drugs is more important to enhance the efficacy of the drug for cancer treatment.

Bursehernin or 5′-desmethoxyyatein (Fig. 1) is a lignan that found in *Bursera fagaroides*, *Macrococculus pomiferus*, *Bursera simaruba* Sarg., *Linum meletonis* and *Geranium thunbergii* [8–12]. The bursehernin have shown potent cytotoxic activity in many cancer cell lines including nasopharyngeal, prostate, breast and colon cancer cell lines [13]. Moreover, this compound shows the cytotoxicity effect against HT-29 (human colon) cells with IC_{50} values of 0.40 ± 0.001 and 0.41 ± 0.01 μg mL^{-1} after incubation at 48 and

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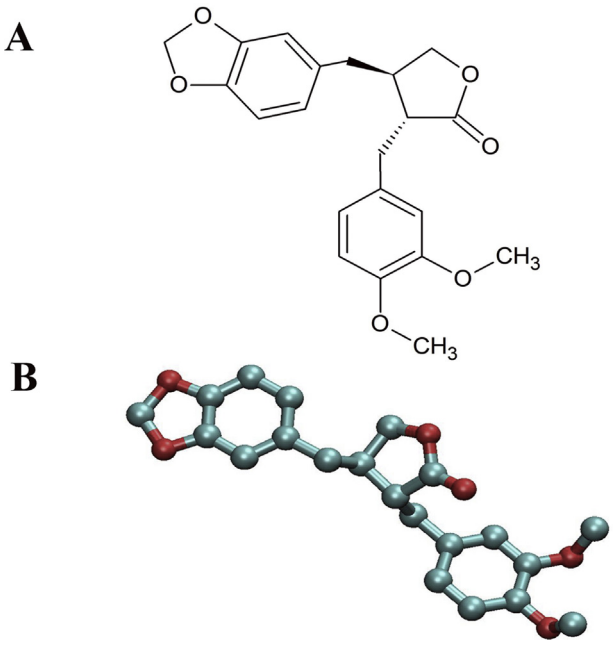

Fig. 1. 2D (A) and 3D (B) structure of bursehernin.

72 h, respectively [8]. However, the molecular mechanism and protein target in cancer inhibition are remains unclear.

Currently, computational technique is a powerful tool to predict the binding mode and binding affinity of the protein target and a ligand. Computational tool is a useful and effective of modern structure-based drug designing in term of cost saving and decrease time consuming. The structure of the target proteins in cancer pathway can be obtained from the protein data bank (PDB). This tool can predict the orientation of the ligand-protein complex in a stable form and its activities.

In this study, our attempt is to identify bursehernin molecular targets associated with cancer occurrence/progression. Its binding affinity of bursehernin to each interested target protein was evaluated using molecular docking method and the molecular information of bursehernin-protein complex was investigated using molecular dynamics (MD) simulation.

2. Computational details

2.1. Protein structure preparation

Eighty crystal structures of cancer-related proteins, in a monomeric form, were obtained from the RCSB Protein Data Bank (www.rcsb.org) [14]. All crystal structure possessed a resolution of less than 3.5 Å. The ligand or inhibitor was removed from the structure prior to the docking procedure using Visual Molecular Dynamic (VMD) package [15]. An ion(s) covalently bound to the protein was retained and all atoms were selected on the basis of the highest occupancy. Missing polar hydrogens were added based on a protonation state of pH 7. The atomic charge of all ions was manually adjusted on the basis of atomic valency. All procedures were performed using the Autodock Auxilliary Tool (ADT) version 4.1 [16]. The protein structure was eventually saved in a Protein Data Bank (PDB), Partial Charge (Q), & Atom Type (T) (PDBQT) format file.

2.2. Bursehernin structure preparation

Bursehernin 3D-structure was obtained from the PubChem ligand structure database (www.pubchem.ncbi.nlm.nih.gov) shown in Fig. 1, and eventually written in the Protein Databank (PDB) file format using Chimera program version 1.10.1. All of polar hydrogen atoms were added by the Autodock Auxilliary Tool (ADT) version 4.1. Finally, the structure was saved in a PDBQT format file.

2.3. Inhibitor structure preparation

An inhibitor was directly adopted from the crystal structure. Polar hydrogen atoms were added. A total molecular charge of inhibitor structure was adjusted according to its normal charge. All inhibitors were performed during this process using the Autodock Auxilliary Tool (ADT) version 4.1 and were finally written in the PDBQT file format.

2.4. Molecular docking study

The molecular docking study was operated using the Lamarckian genetic algorithm implemented using AutoDock4 version 4.2 [16]. The docking protocol was as follows: 50 docking runs with a population size of 200. Other parameters followed the default values in the Autodock4 package. The lowest binding energy (ΔG_{bind}) and the corresponding inhibitory constant (K_i) were reported. The docked conformations were then clustered using an RMSD tolerance of 3.0 Å.

2.5. Molecular dynamics study

Molecular dynamics (MD) simulations were performed on the FMS kinase receptor and inhibitors to investigate the dynamic nature of interactions and dissect the comparative between bursehernin and known inhibitors. The structure of the FMS kinase inhibitor (P31) and bursehernin was optimized using Gaussian09 [17] for the calculations of RESP partial charges. Next, the protein structure was performed using to prepare protein protocol implemented in Discovery Studio to determine protonation state of any ionizable sidechain. MD simulations were then performed using the PMEMD module implemented in the AMBER16 package [18]. Briefly, each system was solvated by TIP3P water molecules followed by the addition of Na^+ and Cl^- counter ions to neutralize the system, yielding a concentration of 0.15 mol dm^{-3}. The system was equilibrated in a canonical ensemble (NVT), using Langevin Dynamics as a thermostat set at 310 K (37 °C) for 500 ps. The system was then switched into isothermal and isobaric (NPT) ensemble with a pressure of 1.013 bar (1 atm) in order to mimic an *in vivo* environment, using Berendsen algorithm. MD simulations were run for 100 ns time scale under constant temperature (310 K) and pressure (1 atm) using a time step of 2 fs. The stability and time dependent behavior were investigated at different nano-scale intervals and analyzed using ptraj module and VMD package. The first 60 ns-simulation was omitted and the 400 snapshots from the last 40 ns were taken for analysis.

The binding energy of the compound with respect to FMS was evaluated from molecular mechanics/Poisson-Boltzmann surface area (MM/PBSA) approach, implemented in AMBER16 package. The equidistant 200 snapshots from the last 40 ns simulation were exploited to compute the binding energy in a unit of Kcal mol^{-1}.

3. Results and discussions

3.1. Docking analysis

Overall of 80 proteins in cancer pathway were screened and predicted the binding mode with bursehernin compound by performing molecular docking calculations (Table 1). The RMSD values of re-docking comparing to crystal structure are considered as a measure of the accuracy of the docking results. The optimal pose is recognized if its RMSD value is found to be less than 3.0 Å. If