Screening for anti-angiogenic natural inhibitors for vascular endothelial growth factor receptor-An Insilco approach

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Abstract

Angiogenesis is the formation of new blood vessels. Angiogenesis is a process controlled by certain chemicals produced in the body. Some of these chemicals stimulate cells to repair damaged blood vessels or form new ones. Other chemicals, called angiogenesis inhibitors, signal the process to stop. Angiogenesis inhibitors usually have only mild side effects and are not toxic to most healthy cells. In our study attempt was made to find potent anti-angiogenic inhibitor for vascular endothelial growth factor receptor using natural agents targeting biological processes important in cancer. One group of growth factor receptors critically implicated in angiogenesis is vascular endothelial growth factor receptors. VEGFR2 kinase domain in complex with a benzisoxazole inhibitor is served as a molecular target for our study. The investigational anti-angiogenic inhibitor Pazopanib was considered as a reference drug in this work. Four substances have been approved to control angiogenesis in the therapy of renal cell carcinoma: Sunitinib, Sorafenib, Temsirolimus, as well as a combination of bevacizumab and interferon alpha. Other substances, such as Everolimus, Pazopanib and Axitinib, are currently the subject of clinical trials. Hundreds of natural molecules were selected from various scientific articles. The initial screening of the molecules based the lipinski’s rule of five. Molecules which were satisfying this rule were taken for receptor-ligand interaction study using docking tools HEX and Quantum. Around fifteen molecules were taken as lead molecule and its binding pocket on VEGFR2 was analyzed using SwissPDBviewer and Q-site finder. The molecules which were interacting with VEGFR2 were taken for pharmacokinetics study using ADMET tools. Ames test of the molecules was predicted for probability of mutagenicity on molecular system. Health effects of these molecules in blood, cardiovascular system, gastrointestinal system, kidney, liver and lung were considered for further screening of the molecules. The natural molecules Curcumin, Epigallocatechin gallate (EGCG), Barringtogenol and Finasteride were showing reliable interaction with VEGFR2 and their pharmacokinetics parameters were comparatively good than the pazopanib. The dietary product curcumin and epigallocatechin gallate (EGCG) can be cancer chemopreventive agents and the natural molecules and Finasteride can be effective inhibitors for vascular endothelial growth factor receptor.