

## IN SILICO APPROACH OF ANTICANCER ACTIVITY OF PHYTOCHEMICAL COUMARINS AGAINST CANCER TARGET JNKs

ROHINI Ka,\* , SRIKUMAR P Sb

<sup>a</sup>Unit of Biochemistry, <sup>b</sup>Unit of Psychiatry, Faculty of Medicine, AIMST University, Semeling, Bedong, Kedah, Malaysia.  
Email: rohinik23@gmail.com

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### ABSTRACT

**Objective:** Phytochemicals are the secondary metabolites of medicinal plants and are considerably used in traditional cancer research. *Homo sapiens*-Jun NH2-terminal kinases (JNKs) are enzymes critical in chronic diseases. JNKs are proteins best known for its role in the activation of the c-Jun/activator protein-1 (AP-1) transcription-factor complex. Targeting JNKs inhibition might initiate the clinical benefits in chronic disease like cancer.

**Methods:** In silico approach is an attempt at identifying the anticancer activity of phytochemical coumarins from medicinal plants against the cancer target *Homo sapiens* JNKs. The dataset comprising of coumarins compounds obtained from medicinal plants like *Psoraleacorylifolia* and *Selinummonniere* were used for virtual screening in AutoDock Vina and molecular docking in AutoDock.

**Results & discussion:** The results of virtual screening of coumarins showed the predicted binding affinity towards JNKs binding site. Among the phytochemicals screened, hit compounds imperatorin and osthol was further docked to confirm the binding mode and confirmed the effective inhibition of JNKs and anticancer activity.

**Conclusion:** Our study suggests that the potential use of phytochemicals imperatorin and osthol from *Selinummonniere* may act as better leads and in turn prevent cancer.

**Keywords:** Phytochemicals; JNKs; Coumarins; Virtual screening; Molecular docking.

### INTRODUCTION

Mitogen activated protein kinase are the family of conserved signal proteins which regulate various cellular process[1]. One of the subfamily proteins, c-jun NH2-terminal kinases (JNKs) are a group of serine/threonine protein kinases[2]. JNK significant role is to regulate cellular processes like proliferation, differentiation and growth. The process of JNKs activation is mainly by inflammatory signals and stressors and is critical for expression levels in human tumors and cancer cells[3]. Up-regulation of JNKs level plays an important role in various cancers such as liver and prostate[4]. For neoplastic transformation and skin tumor formation in mice, JNKs are best known proteins for activation of c-Jun/activator protein-1 (AP-1) transcription-factor complex[5]. JNK signaling pathway has been a great importance for researchers in therapeutic targeting. Coumarins are common phytochemical with large class of compounds found in plant kingdom[6]. Coumarins, classified as a member of the benzopyrone family of compounds, consist of a benzene ring joined to a pyrone ring. Coumarin sub-types are simple coumarins, furanocoumarins, pyranocoumarins and pyrone-substituted coumarins[7]. Due to its specific biochemical properties, coumarins have great value in clinical medicine and are used for the treatment of clinical diseases.

### MATERIALS & METHODS

#### Virtual screening

In drug design protocol, virtual screening is becoming a powerful method for hit and lead discovery. Virtual screening can be done either based on structure or ligand. In this study, structure based virtual screening was followed. The dataset of five phytochemical coumarins is selected from PubChem database. The 2D and 3D structures are constructed and used for virtual screening (Fig 1). AutoDock Vina, a standard tool for virtual screening was used. The average accuracy of binding prediction was increased by assume docking as a stochastic global optimization of the scoring function, precalculating grid maps and precalculating the interaction between every atom type pair at every distance and Vina using input files in PDBQT format of both receptor and ligand. The size of the grid box is key parameter in AutoDock. The volume of the box was fixed to 27000Å<sup>3</sup> to have large search space. The parameter exhaustiveness

made search algorithm better for accurate binding prediction. The results of Vina showed the binding affinity in kcal/mol (Table 1).

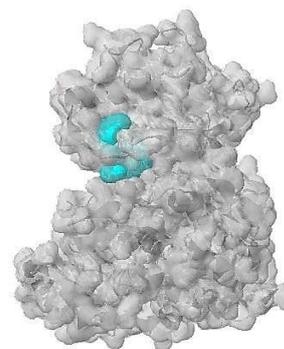


Fig. 1: Binding site of JNKs predicted in Q-sitefinder and visualized in surface.

Table 1: Virtual screening results from AutoDock Vina

S. No.	Compound	Binding affinity kcal/mol
1	Coumarin	-4.5
2	8-Methoxypsoralen	-5.4
3	Imperatorin	-6.0
4	Osthol	-5.6
5	Psoralen	-5.2

#### Molecular docking

Molecular docking is a method to confirm the binding mode and interaction energy for the ligands with the target protein. For the hits imperatorin and osthol, molecular docking was carried out in AutoDock 4.0. Based on predicted binding residues, grid box was constructed and molecular docking was performed using tools like autogrid and AutoDock (Fig 2a & 2b). The results were analyzed based on least binding energy among the top ten conformation of the ligand. The H-bond interaction was analyzed in PyMol. The number of H-bonds was calculated with bond length between atoms of protein-ligand docked complex.

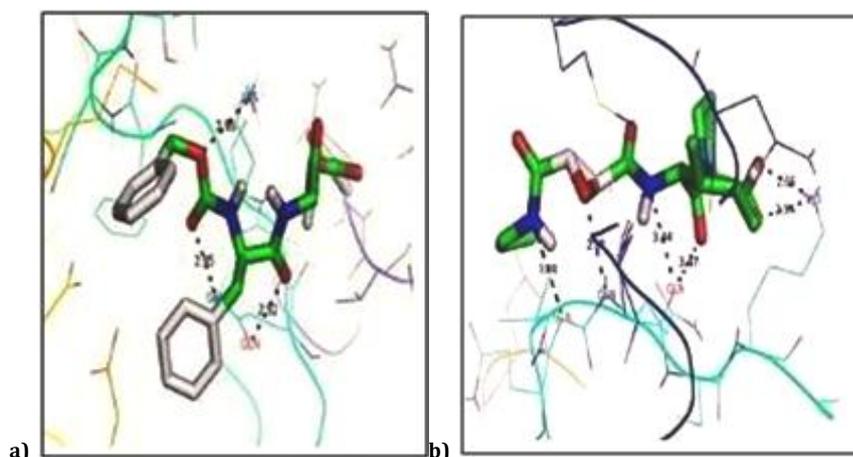


Fig. 2: a) Docked complex of imperatorin and H bond visualized in dots with bond length. b) Docked complex of osthol.

### ADMET

Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties of drug candidates play a key role in drug discovery and environmental hazard assessment. The ADMET structure-activity relationship server, (admetSAR), is a comprehensive knowledge and tool for predicting ADMET

properties of drug candidates and environmental chemicals. The admetSAR server provides a user-friendly interface to easily search a chemical profiles, by CASRN, common name and similarity search. In addition, 30 high predictive QSAR models were implemented in admetSAR for new chemical ADMET properties in silico filtering (Table 2). URL: <http://www.admetexp.org>.

Table 2: ADMET results

S. No.	Compound	Blood-Brain Barrier penetration	% Human Intestinal Absorption	Caco-2 Permeability
1	Coumarin	BBB+	HIA+	Caco2+
2	8-Methoxypsoralen	BBB+	HIA+	Caco2+
3	Imperatorin	BBB+	HIA+	Caco2-
4	Osthol	BBB+	HIA+	Caco2+
5	Psoralen	BBB+	HIA+	Caco2+

### RESULTS & DISCUSSION

Phytochemicals are widely and effectively used in treatment of various diseases in traditional medicinal treatment and phytophysical properties of coumarins have been extensively studied[8]. The treatment of chronic disease like cancer with phytochemicals is critical in the research studies[9]. Our in silico approach on phytochemicals coumarins against cancer target JNKs is carried out using virtual screening, molecular docking and ADMET methods. Virtual screening of five coumarins compounds showed the binding affinity towards target JNKs. The compounds were screened with least binding affinity and compounds imperatorin and osthol were selected as hits. The molecular docking of the two hits showed the binding mode and interaction energy. H-bond pattern was analyzed and confirmed the inhibition of cancer target JNKs to show the anticancer activity of phytochemicals coumarins. Our report based on in silico studies, concluded that coumarins of imperatorin and osthol inhibit JNKs and possessed better anticancer activity against JNKs. Further studies on leads imperatorin and osthol can be done in experimental studies to confirm the inhibition and may be used in the treatment of cancer.

### REFERENCES

- Johnson GL, Lapadat R. Mitogen-activated protein kinase pathways mediated by ERK, JNK and p38 protein kinases. *Science* 2002;298:1911-1912.
- Martin JH, Mohit AA, Miller CA. Developmental expression in the mouse nervous system of the p493F12 SAP kinase. *Brain Res Mol Brain Res* 1996;35:47-57.
- Wagner EF, Nebreda AR. Signal integration by JNK and p38 MAPK pathways in cancer development. *Nat Rev Cancer* 2009;9:537-549.
- Chang Q, Zhang Y, Beezhold K J, Bhatia D, Zhao H, Chen J, et al. Sustained JNK1 activation is associated with altered histone H3 methylations in human liver cancer. *J. Hepatol* 2009;50:323-333.
- Dong Z, Birrer MJ, Watts RG, Matrisian LM, Colburn NH. Blocking of tumor promoter induced AP-1 activity inhibits induced transformation in JB6 mouse epidermal cells. *Proc. Natl Acad. Sci USA* 1994;91: 609-613.
- Lake B. Synthesis & pharmacological investigation of 4-hydroxy coumarin derivatives & shown as anti-coagulant. *Food ChemTox* 1999;3:412-423.
- Aoife Lacy, Richard O'Kennedy. Studies on coumarins and coumarin-related compounds to determine their therapeutic role in the treatment of cancer, *Current Pharmaceutical Design* 2004;10:30.
- Bakkialakshmi S, Menaka T. Study on the solid inclusion complex of coumarin-1 with  $\gamma$ -cyclodextrin. *Int J Pharm Pharm Sci* 2012;4(4): 4, 63-68.
- Saju Thomas, Seetha Devi B. Phytochemical and *in vitro* anthelmintic studies of hydro-alcoholic extract of *Costus pictus*. *Int J Pharm Pharm Sci* 2013;5(3):639-641.