Herbal Therapeutics: Biochemical and Biotechnological Interventions

Dr. Sebastian Vadakan
Dr. Sudeshna Menon
Dr. Dweipayan Goswami

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ARCHERS & ELEVATORS PUBLISHING HOUSE

131 AGB Lay out, 6th Cross

Hesaraghatta Main Road

Bangalore-560090 (INDIA)

Mob: + 91 9164362263

E-mail: archerselevators@gmail.com

Website: www.aeph.in

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Contents

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In silico studies of potent inhibitors of DYRK1A

Sreejith Nair[a], Zankruti Dholakia[b], Divya Chandel[a*]

Down syndrome (DS) also commonly known as Trisomy 21, Trisomy q and Mongolism (in former times) is a set of mental and physical problems that occur due to chromosomal aberrations. Down syndrome is the leading cause of intellectual disability which comes with a huge medical and social cost. It occurs in 1/700 live births in all ethnic groups. DYRK1A is a homology of the *Drosophila melanogaster* minibrain (MNB) protein kinase which is essential for normal post embryonic neurogenesis (Park 2009). The protein has multiple biological function and is visible in its interaction with various cytoskeletal, synaptic and nuclear proteins. Initial evidences have been discovered in favour of the role of MNB/DYRK1A in neuronal development from the study of MNB mutant of Drosophila. The MNB mutant flies showed smaller brain development. Structure Based Drug Design (SBDD) is a system that refers to the systematic use of structural data which is either obtained through experiments or via homology modelling. The aim of SBDD is to prepare ligands with specific electrostatic and stereochemical properties so as to achieve high receptor binding affinity. The designed molecules were tested for toxicity parameters and examined for interaction with DYRK1A.

Keywords *Down syndrome, Trisomy 21, minibrain (MNB), DYRK1A, structure based drug designing (SBDD)*

Introduction

Trisomy in chromosome 21 gives rise to Down syndrome, one of the common genetic disorder with an occurrence of 1 in every 700 births (Hydar and Reeves, 2012). The condition arises from partial or complete duplication of chromosome 21, where some of the genes present in Down syndrome critical region are believed to be responsible for causing Down syndrome. An extra copy of chromosome causes imbalance in gene expression, causes distinct facial appearance, hypotonia, congenital heart defects, mental retardation, early onset Alzheimer's disease (AD), susceptibility to leukaemia, gastrointestinal malformations, and immune system defects. Among more than 30 different genes located on DSCR (Down Syndrome Critical Region), DYRK1A (Dual-specificity tyrosine phosphorylation-regulated kinase) is associated with symptoms like cognitive disabilities, mental retardation as well as some neurodegenerative diseases like AD, Parkinson's disease. It has been observed that DYRK1A is responsible for inducing NFAT (Nuclear Factor Activated T-cells) pathway, however, 1.5-fold increase of DYRK1A leads to reduction in NFAT translational activity thereby causing dysregulation of vertebral development (Park et al, 2009). DYRK1A is a member of kinase family and it is found to phosphorylate the APP and Tau protein responsible for causing AD (Gaurdin et al, 2013). Several compounds have been isolated which shows inhibitory effect on DYRK1A. Natural compounds like beta carboline indole alkaloids are known to be potent inhibitors of DYRK1A. Epigallocatechin-3-gallate, a flavonoid is a potent non-competitive inhibitor where as Harmine, beta carboline indole alkaloid is a potent competitive inhibitor which binds at ATP binding site of DYRK1A. Beta carboline indole alkaloids cause major side effects like hallucinations (Park et al, 2009). Harmine, which is a potent inhibitor of DYRK1A is also known to have an inhibitory effect on mono amine oxidase, which in turn makes the compound hallucinogenic. Computational approach of docking is very helpful in new lead discovery and its pharmacognosy in various field. Here in, the interactive characteristics of known inhibitors were studied, based on which a computer-based structure was designed, which can potentially inhibit DYRK1A with less toxicity. DYRK1A was targeted to reduce the mental cognitive disability.

Material and Methods

The study was accomplished by using computational approach which involved ligand-receptor docking studies, protein preparation and analysis of result using visualizing tools. Several online resources and software were used for the implementation of the computational approach. Docking was performed by using two types of approaches, with the first approach being to perform blind docking to see the interactive property of structures. Blind docking was carried out with the help of Hex 8.0 (A.W. Ghoorah M. Smail-Tabbone M.-D. Devignes D.W. Ritchie 2013, http://hexserver.loria.fr) and AutoDock 4.2 (Morris G. M. Huey R. Lindstrom W. Sanner M. F. Belew R. K. Goodsell D. S. and Olson A. J. 2009) was used to find out the exact interaction site of the

[a] Department of Zoology, Biomedical technology, Human genetics, Gujarat University, Ahmedabad-380009
[b] Department of Biochemistry and Biotechnology, St. Xavier's College (Autonomous), Ahmedabad, Gujarat 380009, India.
Email Id: divya_chande@yahoo.com