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DOCKING STUDIES FOR DRUG SULFASALAZINE WITH RUNX1 AND PTPN22 GENE CODING PROTEIN OF RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid Arthritis is an inflammatory autoimmune disease mainly affected to various joints of the human body. This disease is due to the activity of certain genes such as TNFR2,PAD14,SLC22,RUNX1 and PTPN2 2 . This disease is not curable due to its genetic nature. But this can be managed successfully by using certain drugs, among this Sulphasalazine is a potent anti inflammatory drug commonly used to control inflammation of joints. Now there is a need to understand the inner mechanism of the disease at molecular level. This genomics, proteomics and bioinformatics. Hence based on the above concept , in this dissertation attempts have been made to understand the molecular mechanism between genes responsible for Rheumatoid Arthritis and Sulphasalazine by using bioinformatics tools to know the gene and drug interaction. The results obtained from this docking studies clearly indicated that the binding region in RUNX1 to Sulphasalazine drug is 2,where as the binding score is 13%,simultaneously the binding region in PNPN22 IS 7 and binding score is 62%.This means the Sulfasalazine effectively inhibits thePTPN22 gene activity compared with RUNX1 gene of Rheumatoid Arthritis. This study may be helpful to develop a molecular pipeline for new drug discovery.

Keywords: *Sulfasalazine, Runki, Rheumatoid Arthritis*

1.INTRODUCTION

Rheumatoid arthritis is an inflammatory disease that causes pain, swelling, stiffness, and loss of function in the joints (NIAMS,2008) and characterised by fatigue, occasional fevers, and a general sense of not feeling well (Strand and Singh,2007) . As rheumatoid arthritis progresses, the inflamed synoviam invades and destroys the cartilage and bone within the joint and leads to the immobility of the patient.

According to (Helmick et al, 2008, the following genetic factors are responsible for rheumatoid arthritis. Scientist have discovered that certain genes known to play a role in the immune system are associated with a tendency to develop rheumatoid arthritis (Snaevar et al, 2007) reported that an association with in five genes namely TNFR2, PAD14, SLC22, RUNX1, and PTPN22 are responsible for rheumatoid arthritis in human.

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Sulfasalazine is a potent anti-inflammatory drug commonly used to treat o the inflammatory consequences of Chron,s diseases and rheumatoid arthritis (o'dell JR et al,2006), (Plosker et al,2005). Sulfasalazine modulates immune responses by altering macro phage and T cell responses (Liptay S, et al, 1999),(Weber et al, 2000). Many effects have been related to its function as a protein inhibitor (Weber et al, 2000).

Most of benetical effects of sulfasalazine are altriberted to its function of a potent inhibitor NF-KB. Sulfasalazine deirectly inhibits the activity of inhibitor of NF-KB. Sulfasalazine directly inhibitor of KB kinase, effectively preventing down stream KB-depenent transcription event(Weber et al,2000.,Wahl et al,1998). Recent clinical studies have confirmed that the beneficial affects of sulfasalazine in patient with rheumatoid arthritis are in fact related to inhibition of NF-KB activation in the mucosa, which results in reduced cytokine production, and less several inflammation (Chen et al,2003).

Recent advances in genomics, proteomics and computational biology present new way to understand illness. (Yamanaka et al, 2013). For the first time in history, scientists are beginning to understand the inner working of human diseases at the molecular level. (Snaevar et al, 2007). The task of

discovering and developing safe and effective drug is even more promising as our knowledge of disease increases. Before any potential new medicine can be discovered, scientist work to understand the disease to treated as well as possible and to unravel the underlying cause of the condition (Lixie et al, 2009). They try to understand how the gene are altered, how that affects the proteins they encode and how those proteins interact with each other in living cells, how those affected cell change the specific tissue they are in and finally how the disease affect the entire patient. This knowledge is the basis of treating problems (Paolini et al, 2006). Hence in this dissertation attempts have been made to identifying genes which are responsible for rheumatoid arthritis and bind strength of sulfasalazine drug was investigated using Bioinformatics tools.

2.MATERIALS AND METHODS

Computer aided drug design is a specialized discipline for the study of simulation of a ligand –receptor interactions and strongly dependent on bioinformatics tools ,applications and data base. The molecular docking studies were performed by adopting the method of Sanjay et al , (2016) . The following is the description of software , hardware and bioinformatics tools used in this study.

HARDWARE CONFIGURATIONS

Processor	:	Corei5
Hard disk	:	500 GB SATA
RAM		:4 GB DDR3 RAM
Key board	:	LOGITECH Multimedia
Monitor	:	794 MG SAMSUNG LED
DVD drive	:	SONY 52 MAX
Mouse	:	LOGITECH
Printer	:	HP Laser 1005

SOFTWARE TOOLS REQUIREMENTS

Structure Retrieval :NCBI

Drug Structure :DRUGBANK Database

Docking :AUTODOCK Ver.4.0

TOOLS DESCRIPTION

NCBI

The National Center for Biotechnology Information (NCBI) is part of the United States National Library of Medicine (NLM), a branch of the National Institutes of Health. The NCBI is located in Bethesda, Maryland and was founded in 1988 through legislation sponsored by Senator Claude Pepper.

The NCBI houses genome sequencing data in GenBank and an index of biomedical research articles in PubMed Central and PubMed, as well as other information relevant to biotechnology. All these databases are available online through the Entrez search engine.

DRUGBANK Database

The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information. The database contains 6718 drug entries including 1455 FDA-approved small molecule drugs, 131 FDA-approved biotech (protein/peptide) drugs, 86 nutraceuticals and 5076 experimental drugs. Additionally, 4235 non-redundant protein (i.e. drug target /enzyme /transporter/carrier) sequences are linked to these drug entries. Each DrugCard entry contains more than 150 data fields with half of the information being devoted to drug/chemical data and the other half devoted to drug target or protein data.

DrugBank is supported by David Wishart, Departments of Computing Science & Biological Sciences, University of Alberta. DrugBank is also supported by The Metabolomics Innovation Centre, a Genome Canada-funded core facility serving the scientific community and industry with world-class expertise and cutting-edge technologies in metabolomics.

AutoDock

AutoDock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure. Current distributions of AutoDock consist of two generations of software: AutoDock 4 and AutoDock Vina.

AutoDock 4 actually consists of two main programs: *autodock* performs the docking of the ligand to a set of grids describing the target protein;*autogrid* pre-calculates these grids. In addition to using them for docking, the atomic affinity grids can be visualized. This can help, for example, to guide organic synthetic chemists design better binders.

AutoDock Vina does not require choosing atom types and pre-calculating grid maps for them. Instead, it calculates the grids internally, for the atom types that are needed, and it does this virtually instantly. They have also developed a graphical user interface called AutoDockTools, or ADT for short, which amongst other things helps to set up which bonds will treated as rotatable in the ligand and to analyze dockings.

AutoDock has applications in:

- X-ray crystallography;
- structure-based drug design;
- lead optimization;
- virtual screening (HTS);
- combinatorial library design;
- protein-protein docking;
- chemical mechanism studies.

AutoDock 4 is free and is available under the GNU General Public License. AutoDock Vina is available under the Apache license, allowing commercial and non-commercial use and redistribution.

3.RESULTS

Result of NCBI genes RUNX1 and PTPN22 responsible Rheumatoid arthritis in human (*Homo sapiens*)

RUNX1

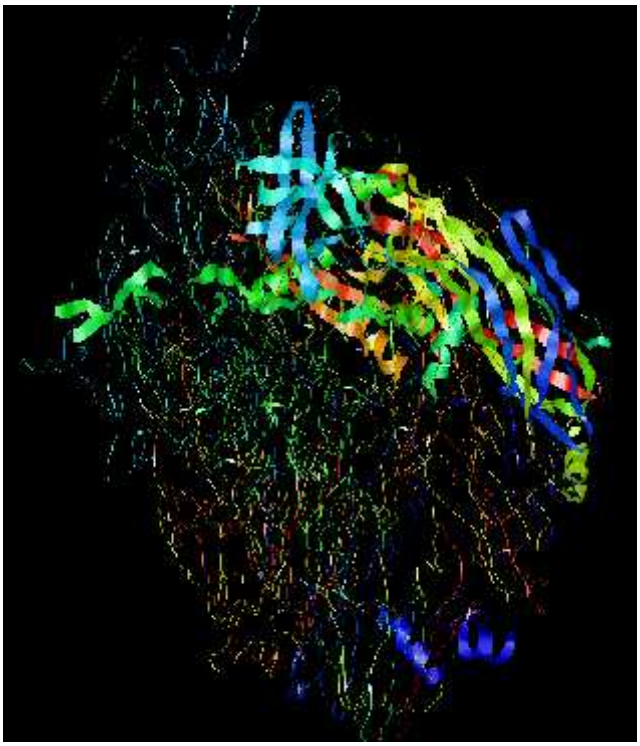

Figure-1

OFFICIAL FULL NAME: Runt- related transcription factor 1
SEQUENCE LANGTH: 480 aa
GENE TYPE: Protein coding
ORGANISM: *Homo sapiens*

PTPN22

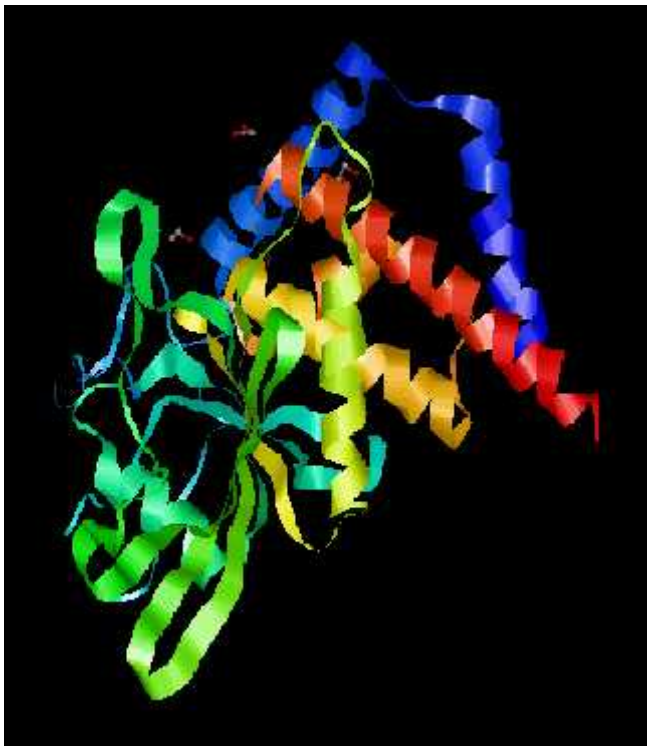

Figure-2

OFFICIAL FULL NAME: Protein tyrosine phosphatase, non-resoptor type 22
SEQUENCE LANGTH: 752 aa
GENE TYPE: Protein coding
ORGANISM: *Homo sapiens*

3D structure of sulfasalazine

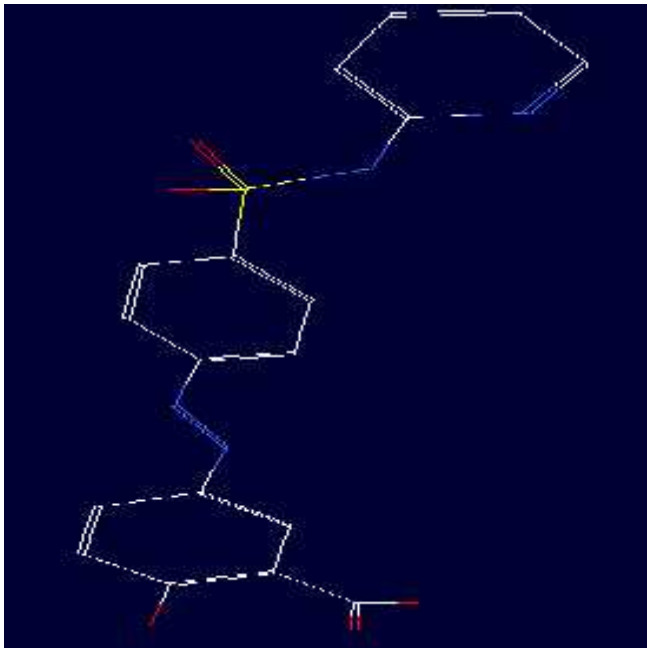

Figure-3

Systematic (IUPAC) name	
2-hydroxy-5-[(*E*)-2-{4-[(pyridin-2-yl)sulfamoyl]phenyl}diazen-1-yl]benzoic acid	
Clinical data	
Trade names	Azulfidine
AHFS/Drugs.com	Monograph
MedlinePlus	a682204

Result of molecular docking of RUNX1 with Sulfasalazine

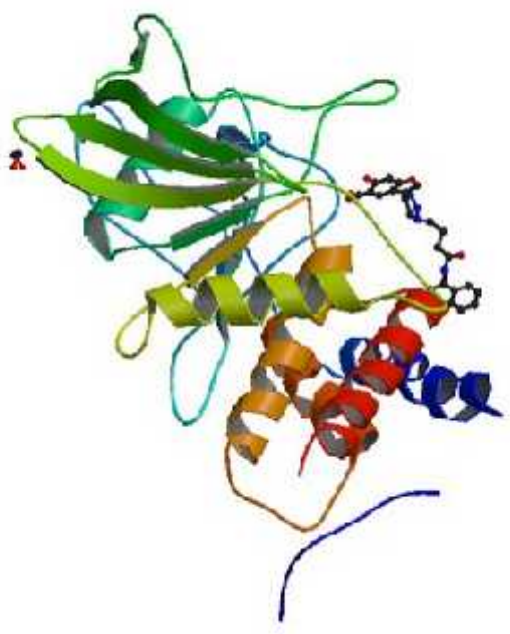

Figure- 4

View Method : Mol. Mechanics
Score value : 13%
Binding Region: 2

Result of molecular docking of PTPN22 with Sulfasalazine

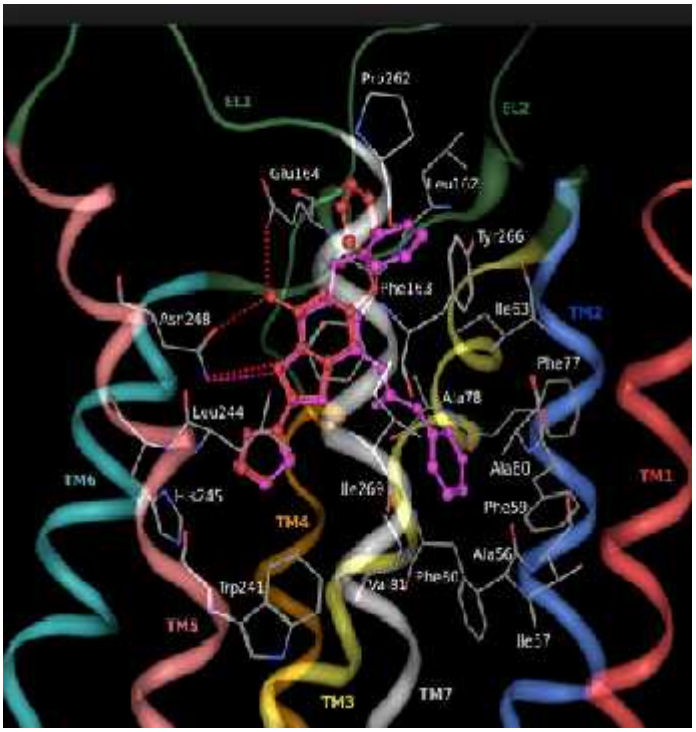

Figure-5

View Method: Mol. Mechanics
Score value : 62%
Binding Region: 7

4.DISCUSSION

Rheumatoid Arthritis is a multifactorial disease due to a combination of genetic and environmental factors. Identification of the genetic factors involved in the pathogenesis of Rheumatoid Arthritis should open as avenues for developing radical treatment strategies directed at the cause of the disease. Recent studies support a role for several genes namely PADI4, $TNFR_2$, SLC22A4, $RUNX_1$, and PTPN22 (Li and Joens, 2001). In this dissertation we collected all 3D structures available for the genes namely RUNX1 and PTPN22, which encoding the proteins responsible for Rheumatoid Arthritis in human, *Homo sapiens* (Fig.1,2). Same time we extracted the 3D structure of sufasalazine, a potent anti – inflammatory drug commonly used to treat the consequences of Rheumatoid Arthritis from Drug Bank database (Fig. 3). The identification of protein ligand interaction networks on a proteome – is crucial to address a wide range of biological problems such as correlating molecular function to physiological processes and designing safe and efficient therapeutics (Kehn et, al, 2008). In this study attempts have been made to developed a computational pipeline for molecular docking of existing drug sulfasalazine and protein targets responsible for Rheumatold Arthrits (Fig, 4 and). The Autodock 4 software is used for the molecular docking of drug and protein target. Recent protein - ligand interaction studies have revealed that protein targets involved in entirely different pharmacology can bind similar small molecule drugs (Weber et al., 2004 and Xie et al., 2007).

From the above molecular docking results it is observed that the binding region for the gene coding protein RUNX1, the binding region for drug sulfasalazine is 2. The strength of binding between protein and drug is 13% (Fig. 4). Finally for the gene encoding protein PTPN22 the binding site for sulfasalazine is 7. The percentage of binding between protein target and drug is 62% (Fig. 5). From this study it is observed that the strength of binding of drug with protein target is low . Hence the expression of gene responsible for Rheumatoid arthritis is not effectively controlled by sulfasalazine. Large scale docking of many protein targets to many drugs will be helpful to identify the more effective drug for Rheumatoid Arthritis.

5.CONCLUSION:

In this study attempts have been made to develop a computational pipeline for large scale molecular docking of generic drug sulfasalazine to protein targets responsible for Rheumatoid Arthritis. Large scale docking of many protein targets to many drugs will be helpful to identify the more effective drug for Rheumatoid Arthritis. This study may be help to develop high – efficacy drugs by inhibiting multiple targets or to reposition existing drugs to treat Rheumatoid Arthritis effectively.

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