International Journal of Latest Trends in Engineering and Technology
Special Issue SACAIM 2016, pp. 213-215
e-ISSN:2278-621X

ANALYSIS OF COMPOUNDS IN GRAVIOLA (ANNONA MURICATA) AGAINST CD20 ANTIGEN FOR NON-HODGKINS LYMPHOMA

Eliza Denise Machado[1] and Hemalatha N[2]

Abstract- Cancer is becoming a common and dangerous disease in the world today. There are over 100 different types of benign and malignant tumors discovered in the human body. Although there are various treatments, it is not always possible to completely cure in the case of malignant cases. Also, most treatments result in various, painful side-effects. Hence, studies are being done to find an alternative.In this work, we have worked with Non-Hodgkin's Lymphoma. The protein file of CD20 antigen was taken, optimized and minimized, using Swiss PDB Viewer. Out of more than 100 phytochemicals, only 79 phytochemicals were chosen. These compounds were drawn and later converted to Protein Data Bank (.pdb) files. These files were then docked against the target protein, using Autodock, with a Lamarckian Genetic Algorithm. The top 5 compounds with the lowest binding energy were selected, and further analyzed. Their molecular properties and other physiochemical properties were analyzed.It was found that cis-annonacinshowed better results.It is not very clear if the phytochemical compounds, in question, will have the same effect on the target protein as a conventional drug. In the future study, confirmation of the study in the wet lab is required.

Keywords –Cancer, Non-hodgkins' lymphoma, Soursop, Phytochemicals, Cd20, Antigen

I. INTRODUCTION

Cancer is a class of diseases characterized by out-of-control cell growth. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected. Almost every tissue in the body can go out of control, and form tumors or cancer, depending on the 'triggers' or factors that activate the 'cancer gene' that everyone has. It can be benign tumors or malignant cancer, and even the healthiest person can be affected.

Non-Hodgkin's lymphoma is a large group of cancers of lymphocytes (white blood cells). They can occur at any age and are often marked by lymph nodes that are larger than normal, fever, and weight loss. They are mainly found in the lymph system (consisting of Lymph, Lymph vessels, Lymph nodes, Spleen, Thymus, Tonsils, Bone marrow).

In the present paper, we have carried a study by taking 15 proteins from this disease, blasted in PDB for similar structures, found active sites and have tried to dock the validated structures with 3 drugs and 2 medicinal plants. The results of the same have been discussed in the section three.

II. RELATED WORK

Berinstein*et al*., worked on association of serum Rituximab (IDEC-C2B8) concentration andanti-tumor response in the treatment of recurrent low-grade orfollicular non-Hodgkin's lymphoma [1]. They concluded that Rituximab is therapeutically effective against B-cell lymphoma. Pharmacokinetic data suggested that certain subsets of patients may possibly benefit from increased dosing and studies to address this are underway.

Rousseaux *et al*., worked on identifying a novel BET bromodomain inhibitor-sensitive, gene regulatory circuit that could control Rituximab response and tumour growth in aggressive lymphoid cancers [2]. They discovered a gene regulatory circuit involving the nuclear factor CYCLON, which characterizes aggressive disease and resistance

[1] *Aloysius Institute of Management and Information technology,Mangalore, Karnataka , India.*
[2] *Aloysius Institute of Management and Information technology,Mangalore, Karnataka , India.*

to the anti-CD20 monoclonal antibody, Rituximab, in high-risk B-cell lymphoma. They concluded that CYCLON was a new MYC cooperating factor that autonomously drives aggressive tumour growth and Rituximab resistance in lymphoma, and that its resistance mechanism would eventually provide a new combination therapy rationale for high-risk lymphoma.

Moghadamtousi et al., conducted a review on the plant Annonamuricata, of the Annonaceae family, by reviewing its traditional uses, isolated phytochemical compounds, and its various biological activities [3]. According to the review, the phytochemical compounds of A.muricata are found to be mainly acetogenins, having various anticancer, anticonvulsant, anti-arthritic, antiparasitic, antimalarial, hepatoprotective and antidiabetic activities. The review concluded by confirming promising developments of the plant's various uses.

Minari et al., worked on analyzing the chemopreventive effect of A.muricata on DMBA-induced cell proliferation of the breast tissues of female albino mice [4]. Qualitative and quantitative screening of ethanolic extracts of the leaves of Annonamuricata were tested on 30 albino mice with DBMA-induced cell-proliferation. It was found that the extracts significantly reduced proliferation in the tissues; however, the results were varied in occurrence among different groups.

Gavamukulya et al., worked on the phytochemical screening, anti-oxidant activity, and anti-cancer potential of Annonamuricata [5]. The results showed that the extracts were found to be rich in secondary metabolites such as alkaloids, saponins, terpenoids, flavonoids, etc. The ethanolic extract of leaves was found to be selectively cytotoxic in vitro to tumor cell lines while it had no cytotoxic effect on normal spleen cells. However, water extracts did not show anticancer or any other effect. They concluded that A.muricata proved to be a promising new agent as an anti-oxidant, and as an anti-cancer agent.

Renaudineau et al., did a review on Rituximab as a monoclonal antibody to CD20 [6]. They found that Rituximab is also useful in a number of autoimmune disorders. Rituximab has a variable efficacy, depending on the maturity and location of the target B cells, nature of the effector cells, pharmacokinetic considerations, time to B cell depletion and time to B cell restoration. However, all test conducted on Rituximab are not necessarily reliable.

III. MATERIALS AND METHODS

A. Obtaining the Target Protein

The target protein, CD20, was selected, and the pdb file was obtained from the RCSB's Protein Data Bank (PDB) web database. Since the CD20 was not available in its original form, the pdb file of the CD20 in a complex with the monoclonal antibody, Rituximab, was obtained. Using Swiss PDB-Viewer, the Rituximab was separated from the complex, isolating the CD20 antigen for further analysis.

Protein Data Bank (PDB) archive (http://www.rcsb.org/pdb/home/home.do) is the single worldwide repository of information about the 3D structures of large biological molecules, including proteins and nucleic acids. These are the molecules of life that are found in all organisms including bacteria, yeast, plants, flies, other animals, and humans. Understanding the shape of a molecule deduce a structure's role in human health and disease, and in drug development. The structures in the archive range from tiny proteins and bits of DNA to complex molecular machines like the ribosome.

B. Obtaining the ligands

The phytochemical compounds of Annonamuricata, were considered as possible ligands for the target protein. The chemical compounds were created by drawing them using ChemSketch tool, and saving them under MOL format. The MOL files of the compounds were later converted to PDB files, using the conversion tool, OpenBabel Around 79 total phytochemical compounds were obtained from Annonamuricata, as described in the review done on the plant's uses, acetogenins and biological activities.

C. Protein optimization and Minimization

The target CD20 protein, was subjected to Optimization and Minimization, to remove unwanted atoms of the previous attached protein, followed by Energy Minimization of the Optimized target protein. This was done by using Swiss PDB-viewer. Once the protein was Optimized, the target protein was ready for docking and analysis.

D. Docking the Protein with the Ligands

The 79 compounds were docked with the target protein, by running them through AutoDock v.4.0. The entire protein was considered when docking the protein with the compounds, as possible ligands.The final autogrid and autodock algorithms were run using Cygwin Terminal software, to obtain the final minimum binding energy of each of the ligands against the protein. The proteins with the lowest minimum binding energy were selected and subjected to screening by checking ADMET properties.

E. Analysis of Properties of Ligands

The compounds which had the lowest minimum binding energy were selected. Their Physiochemical properties, Molecular Properties, Lipinski rule, and more, were analyzed, by running them through the ACD Labs servers. The final results will give a probable idea of an alternative compound that can be used as a drug. “Labor intensive experimental testing and literature searches can be reduced by using the online ACD/I-Lab prediction engine (http://ilab.acdlabs.com/iLab2/) to predict physicochemical properties, NMR spectra and chemical shifts, and ADME toxicities. The browser-based I-Lab software also assesses prediction reliability and includes searchable content databases.

III. RESULTS AND DISCUSSION

A. The Target Protein

The target protein, CD20, was selected and separated from Rituximab, which was in complex with it, as 2OSL.pdb (Fig 1). The resulting protein was used for further analysis. The target CD20 protein, was optimized by removing excess heteroatoms belonging to the rituximab protein. The CD20 protein was then subjected to energy minimization, and then for docking.

B. Docking

The 79 compounds were docked with the target protein, by running them through AutoDock v.4.0. Each ligand was made to dock with the entire CD20, using co-ordinates as X: 27.284, Y: 42.53, and Z: -31.741. The ligands were docked using default parameters, and running them through the Genetic Algorithm. The format was then saved using Lamarckian Genetic Algorithm.

On running the Autogrid and Autodock Algorithm, it was found that the top 5 compounds with the lowest minimum binding energies were: Rutin, Kaempferol 3-O-rutinoside, Kaempferol 3-O-robinobioside, Cis-annonacin and Isolaureline (Fig 2). The other compounds had poor minimum binding energy, and hence, were discarded.

C. Analysis of Properties

The compounds,having the lowest minimum binding energy, were selected. Their Physiochemical properties, Molecular Properties, Lipinski rule, and more, were analyzed, by running them through the ACD Labs servers. The results showed that cis-annonacin gave slightly better results than the other 4 compounds. However, they all had poor bioavailability and probably poor absorption, as none of the selected compounds could be absorbed through active transport. Also, other than cis-annonacin, all of them showed poor absorption through passive transport.

IV. CONCLUSIONS

From the following analysis, it can be concluded that the compound, cis-annonacin, might have a possible use as a drug in the future, for cancer research. However, further studies must be conducted in order to confirm or reject the possibility for the same.

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