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Molecular Interaction Analysis between IFN-Alpha and Anti-Inflammatory Compounds from *Cassia auriculata* Leaves

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KEYWORDS

Cassia auriculata, anti-inflammatory activity, psoriasis, plasmacytoid, IFN-alpha, Autodock.

A B S T R A C T

Cassia auriculata is a plant species, belongs to the caesalpiniaceae family which is traditionally used to treatmany diseases. It is commonly known as Tanners Senna. The plant has been reported to possess anti-pyretic, anti-diabetic, hepatoprotective, anti-microbial and anti-inflammatory activity. The phytochemical analysis shows that *Cassia auriculata* leaves contains bio active compounds such as Apigenin and Luteolin which have more potent anti-inflammatory activity. Psoriasis is one of the most common T-cell mediated auto immune diseases in humans. The plasmacytoid Pre-Dendritic Cells (PDC`s),the natural IFN-alpha producing cells, infiltrate the skin of psoriatic patients and become activated to produce IFN-alpha early during the development of psoriatic skin lesions.Blocking of IFN-alpha signalling or inhibiting the ability of PDC`s to produce IFN-alpha prevents the T-cell dependent development of psoriasis. In silico docking studies were carried out using Autodock 4.2 based on Lamackrian genetic algorithm principle. Apigenin and Luteolin were docked against IFN-alpha. This study revealed that best interactions and binding energy were seen between Luteolin and IFN-alpha. Hence Luteolin may be considered as a strong inhibitor of IFN-alpha and would serve as a natural therapeutic agent against psoriasis.

Introduction

The use of Plants with pharmaceutical properties has received increased interest nowadays from both homeopathic and allopathic branches. These medicinal plants play an important role in public health, especially in developing countries, where it is believed that the intense utilization of plants with therapeutic action does not lead to intoxication (Mossi *et al*., 2009). The cost of drugs in use today is too expensive for the

majority of the population in the third world countries and therefore the search for some cheap sources of antimicrobial substances in nature become inevitable. Plants are good sources for new safe, biodegradable and renewable drugs. The use of plants as therapeutic agents in addition to being used as food is age long (Dutta *et al*., 1994).

*Cassia auriculata*is widely distributed even in poor soil in Sri Lanka, India, Burma and cultivated in tropics (Kirtikar and Basu, 1984). In Indian ethnomedicine it is used as antidiuretic, astringent, antirheumatic, antihelmentic, and anti-inflammatory (Balakrishna *et al*., 2011). *Cassia auriculata* (family: *Cesalpinaceae*) is profoundly used in Ayurvedic medicine as a tonic, astringent and as a remedy for diabetes, conjunctivitis and opthalmia (Joshi *et al*., 2000). It is one of the principle constituents of 'Avaaraipanchagachooranam'- an Indian herbal formulation used in the treatment of diabetes to control the blood sugar level (Brahmachari and Augsti, 1961).

Psoriasis

Psoriasis is the most common autoimmune disease of the human skin, affecting 2% of the population worldwide (Lebwohl *et al*., 2003). Similar to Crohn's disease and rheumatoid arthritis, psoriasis results from an overt self-perpetuating activation of autoimmune T cells (Adorini *et al*., 1997; Davidson, 2001; Lew, 2004). Plasmacytoid pre-Dendritic Cells (PDCs) are a rare cell population in the peripheral blood and secondary lymphoid organs characterized by plasma cell–like morphology and a unique surface phenotype (Liu *et al*., 2005). PDCs represent key effectors in innate antiviral immunity because of their unique capacity to secrete large amounts of IFN-alpha in response to viruses (Siegal *et al*., 1999). Viral infection leads to an active recruitment of PDCs from the blood into peripheral sites of infection (Vanbervliet *et al*., 2003).

There are three scientific observations that suggest a role for IFN-α in psoriasis. First, psoriatic skin lesions demonstrate an activated IFN-α signaling pathway (Fah *et al*., 1995; Schmid, 1994; Suomela, 2004; Van der Fits, 2004). Second, continuous excessive IFN-α/β signaling in IFN regulatory factor (IRF)-2 mice causes an inflammatory skin disease resembling psoriasis (Hida *et al*., 2000). Finally, treatment of psoriasis patients with recombinant IFN-α for unrelated conditions (e.g., viral infections or tumors) can exacerbate psoriasis (Downs *et al*., 2000; Funk, 1991; Ketikoglou, 2005; Pauluzzi, 1993). Therefore it was hypothesized that IFN-α produced by PDCs may contribute to the pathogenesis of psoriasis.

It was found that PDCs infiltrate the normal-appearing skin of psoriatic patients and become activated to produce IFN-α early during the development of psoriatic skin lesions. Furthermore, it was demonstrated that PDC-derived IFN-α is essential in driving the local activation and expansion of pathogenic T cells leading to the development of psoriatic skin lesions. Thus, activation of PDCs to produce IFN-α in the skin of psoriatic patients represents a key innate immune pathway to initiate the autoimmune T cell cascade leading to psoriasis.

Materials and Methods

Uniprot

UniProt is a comprehensive, high-quality and freely accessible database of protein sequence and functional information, many entries being derived from genome sequencing projects. It contains a large

amount of information about the biological function of proteins derived from the research literature(http://www.uniprot.org/).

Protein Data Bank (PDB)

The Protein Data Bank PDB is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. The data, typically obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists are freely accessible (http://www.rcsb.org /pdb/home/home.do).

OPEN BABEL

Open Babel is a free software, a chemical expert system mainly used for converting chemical file formats (O'Boyle *et al*., 2011). Due to the strong relationship to informatics, this program belongs more to the category cheminformatics than to molecular modeling. It is available for Windows, UNIX and Mac OS. It is distributed under the GNU General Public License. Open Babel includes two components, a command-line utility and a C++ library. The command-line utility is intended to be used as a replacement for the original Babel program, to translate between various chemical file formats. The C++ library includes all of the file-translation codes, as well as a wide variety of utilities to foster development of other open source scientific software.

Pymol

PyMOL is an open-source tool to visualize molecules available from (www.pymol.org). It runs on Windows, Linux and MacOS equally well. PyMOL has excellent capabilities in creating high-quality images from 3D structures, it has well developed functions for manipulating structures and some basic functions to analyze their chemical properties. The possibilities to write scripts and plugins as well as to incorporate PyMOL in custom software are vast and superior to most other programs. PyMOL has been written mostly in the Python language (www.python.org), while the time-critical parts of the system have been coded in C. This way, Python programs interact most easily with the PyMOL GUI.

Pubchem

PubChem
(https://pubchem.ncbi.nlm.nih.gov)
(Agarwala *et al*., 2015; Bolton, 2008; Wang, 2009) is a public repository for information on chemical substances and their biological activities. Since launched in 2004 as a component of the Molecular Libraries Roadmap Initiatives of the US National Institutes of Health (NIH), PubChem has rapidly grown to a key chemical information resource that serves scientific communities in many areas such as cheminformatics, chemical biology, medicinal chemistry and drugdiscovery.Pubchem is the database which is used to retrieve the structure of chemical compounds.

ACD/ChemSketch

ACD/Chemsketch is the powerful chemical drawing and graphics package from ACD/Labs software, which will draw molecular structures, reactions and calculate chemical properties very quickly and easily. The three dimensional structures of flavonoids were drawn by Chemsketch.

Molinspiration

Using the Mol inspiration server (http://www.molinspiration.com/) Molecular properties and drug likeness of the compounds was examined on the basis of "Lipinski's Rule of Five" (Lipinski *et al*., 2001). The Lipinski's rule, formulated by

Christopher A Lipinski in 1997 is a rule of thumb to evaluate drug likeness which states that an orally active drug has no more than one violation of following criteria i,e., has not more than 5 hydrogen bond donors, not more than 10 hydrogen bond acceptors, molecular weight below 500 Daltons, partition co-efficient log P less than 5.

Docking

Autodock

Auto Dock is a suite of automated docking tools. The software is used for modelling flexible small molecules such as drug molecules and its binding to receptor proteins of known three dimensional structures (Friesner *et al*., 2004) (http://autodock.scripps.edu/resources/tools)

Results and Discussion

Retrieval of sequence

The sequence of IFN-alpha protein was retrieved by using Uniprot database (http://www.uniprot.org/).The Uniprot ID of IFN-alpha is P48551 and the organism is *Homosapiens*(Human).

Retrieval of structure

Three dimensional structure (Crystal structure) of the IFN-alpha is retrieved from PDB database and its PDB ID is 3S9D.Three dimensional structure is visualized using RASMOL. Pink color showing alpha helix, yellow showing beta sheets, white colors showing turns. (http://www.rcsb.org/pdb/home/home.do).

Ligand preparation

Apigenin and Luteolin are used as the ligands. (PubChem Compound ID of Apigenin: 12358401; Luteolin: 5280445), was retrieved from NCBI PubChem Compound database (Bolton *et al*., 2008)(http://pubchem.ncbi.nlm.nih.gov/).The 2D and 3D structure of the Apigenin and Luteolin was shown in figure 2.1, 2.2 and 3.1, 3.2 respectively.

Table.1 Ligand molecule 2D and 3D structure

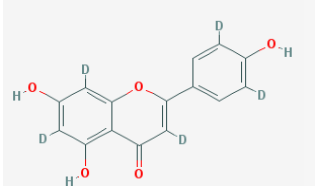
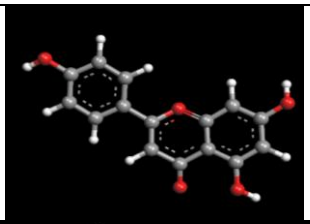
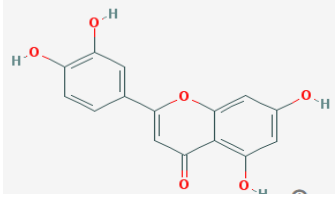
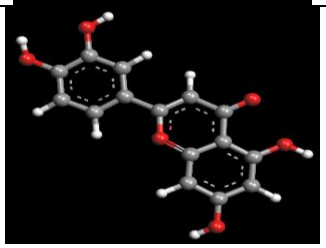
Compound name	2D structure	3D structure
Apigenin		
Luteolin		

Table.2 Lipinski rule of compound molecules

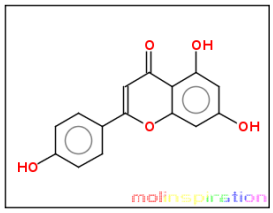
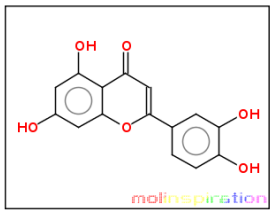
Compound Name	Lipinski`s rule
Apigenin	molinspiration originalSMILES C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O miSMILES Oc3ccc(c2cc(=O)c1c(O)cc(O)cc1o2)cc3  Molinspiration property engine v2014.11 miLogP 2.46 TPSA 90.89 natoms 20 MW 270.24 nON 5 nOHNH 3 nviolations 0 nrotb 1 volume 224.05 Get data as text (for copy / paste). Get 3D geometry BETA
Luteolin	molinspiration originalSMILES C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O miSMILES Oc3cc(O)c2c(=O)cc(c1ccc(O)c(O)c1)oc2c3  Molinspiration property engine v2014.11 miLogP 1.97 TPSA 111.12 natoms 21 MW 286.24 nON 6 nOHNH 4 nviolations 0 nrotb 1 volume 232.07 Get data as text (for copy / paste). Get 3D geometry BETA

Table.3 Shows the interactions between IFN-alpha and Apigenin

IFN-alpha		Apigenin	Distance(Å)	Docking Energy (Kcal/mol)
Residue	**Atom**			
ASP 67	OD2	O	2.6	-4.71
ASP 67	OD2	H	1.9	
GLU 111	OE2	H	1.8	

Table.4 Shows the interactions between IFN-alpha and Luteolin

IFN-alpha		Luteolin	Distance(Å)	Docking Energy (Kcal/mol)
Residue	**Atom**			
ILE 194	N	O	3.1	-7.38
LEU185	O	H	2.1	
ASP 104	O	H	1.9	

Table.5 Overall docking results between IFN-alpha and Flavonoids

S.No	Compounds	Key residues	Binding energy Kcal/mol	No.of hydrogen bonds
1	Luteolin	ILE194(N),LEU185(O), ASP104(O)	-7.38	3
2	Apigenin	ASP67(OD2),ASP67(OD2), GLU111(OE2)	-4.71	2

Fig.1

Fig.2

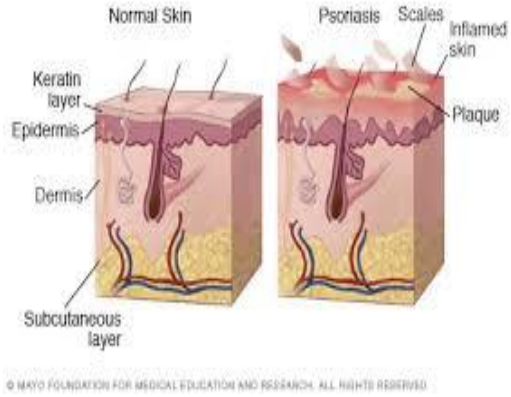


Fig.3 Crystal structure of IFN-Alpha Protein (3S9D)

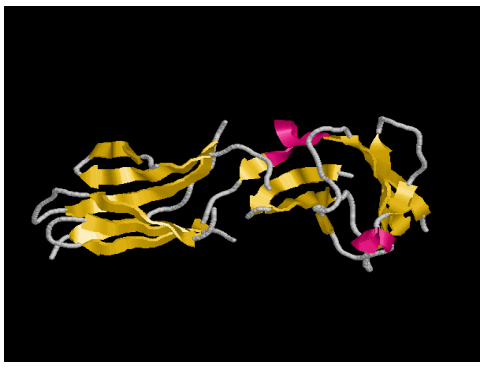


Fig.4 (a) Docking score; (b) Interactions between IFN-alpha and Apigenin visualised using Autodock; (c) Visualisation of hydrogen interactions between IFN-alpha and Apigenin using PyMOL viewer(IFN-alpha:Pink color,Ligand:Blue color,and yellow color dotted lines represent hydrogen bonds)

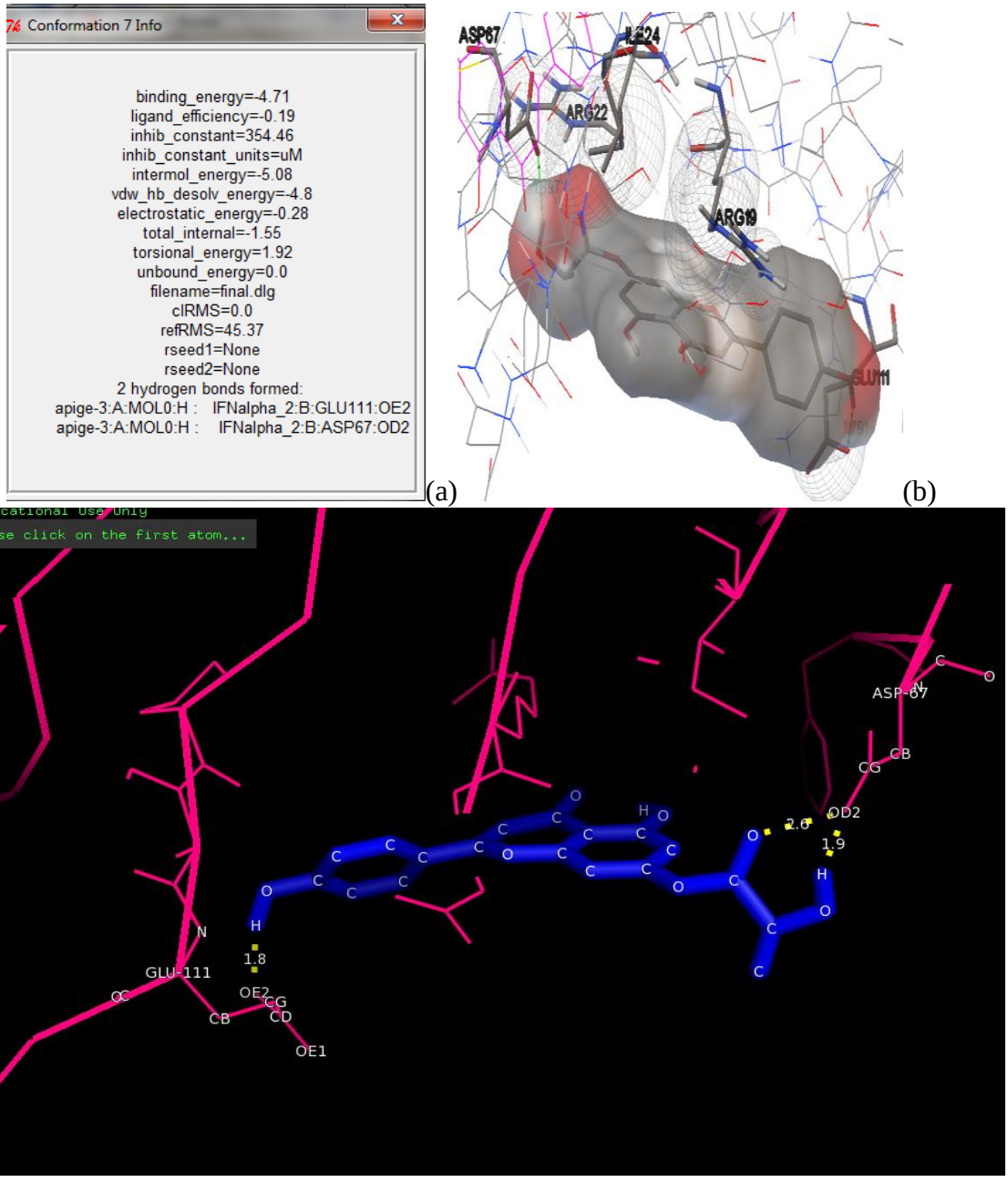
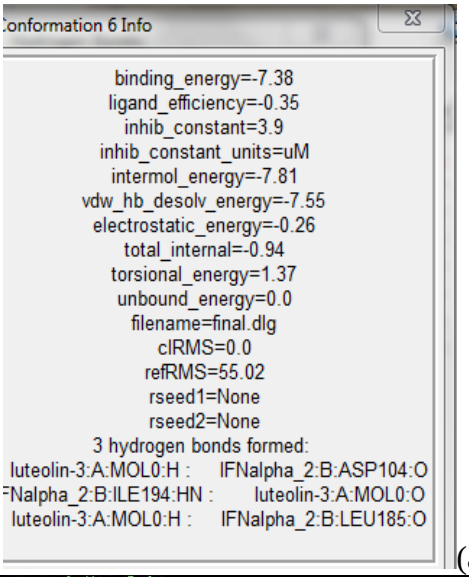
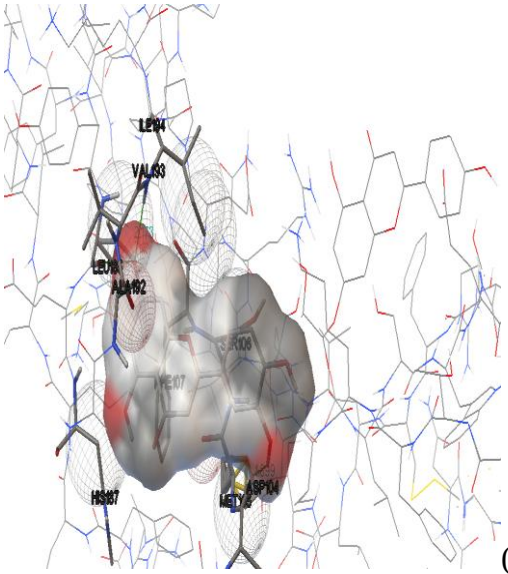


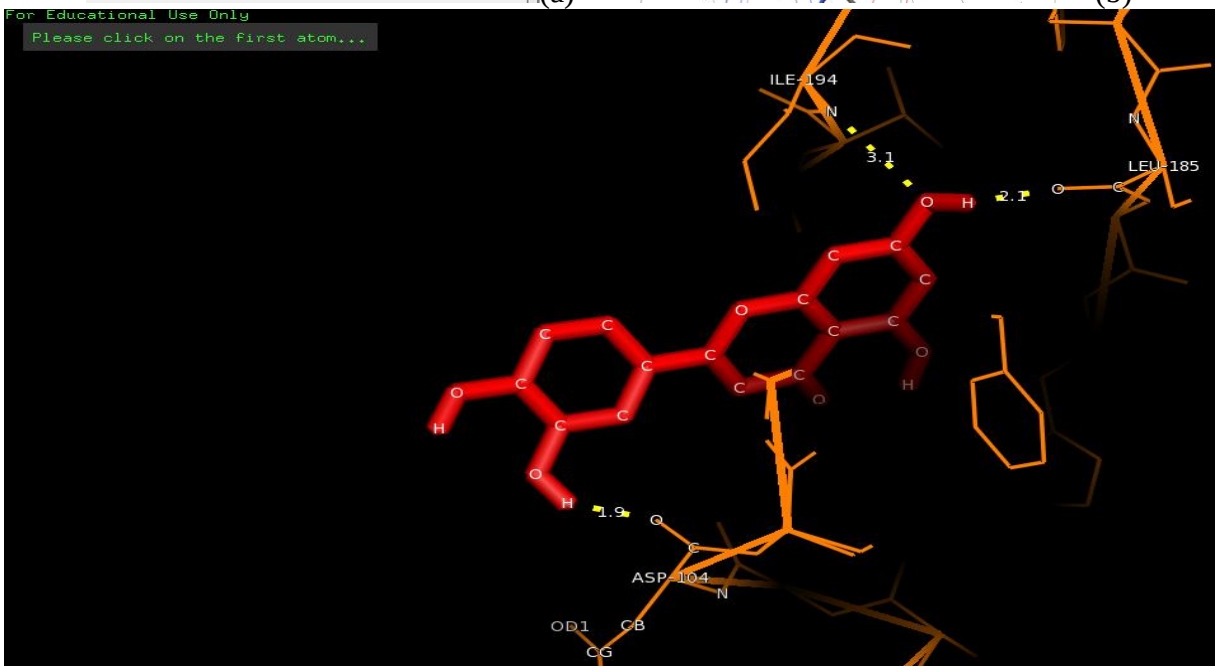
Fig.5 Docking score; (b) Interactions between IFN-alpha and Luteolin visualised using Autodock; (c) Visualisation of hydrogen interactions between IFN-alpha and Luteolin using PyMOL viewer(IFN-alpha:Orange color,Ligand:Red color,and yellow color dotted lines represent hydrogen bonds)



(a)



(b)



(c)

The structure was downloaded in SDF format and was then converted to PDB format using OPEN BABEL 2.2.1(Werner *et al*., 2006) and further used for docking studies.

Docking Analysis of Flavonoids against IFN-alpha

The two flavonoids compounds(Apigenin and Luteolin)are docked against IFN-alpha receptor.The Graphical User Interface

program "Auto-Dock Tools" was used to prepare, run, and analyze the docking simulations. Kollman united atom charges, solvation parameters and polar hydrogens were added into the receptor PDB file for the preparation of protein in docking simulation. AutoDock (Goodsell *et al*., 1996; Jones, 1997; Rarey, 1996) requires precalculated grid maps, one for each atom type present in the flexible molecules being docked and its stores the potential energy arising from the interaction with rigid macromolecules. This grid must surround the region of interest in the rigid macromolecule. The grid box size was set at 126, 126 and 126A° (x, y, and z) to include all the amino acid residues that present in rigid macromolecules. AutoGrid4.2 Program, supplied with AutoDock4.2 was used to produce grid maps. The Lamarckian Genetic Algorithm(LGA)(Morris *et al*.,Goodsell1998) was chosen search for the best conformers. During the docking process, a maximum of 10 conformers was considered. The best ligand-receptor structure from the docked structures was chosen based on the lowest energy and minimal solvent accessibility of the ligand. The flavonoids compounds (Apigenin and Luteolin)and IFN-alpha binding energy are shown in Figures 2a and 3a,final conformations are shown in Figures 2b and 3b,and the interactions visualization using the PyMOL viewer tool shown in Figures 2c and 3c. Hydrogen bond distance between the donor and acceptor atoms are shown in Tables 3 and 4.

The two flavonoids compounds (apigenin and luteolin) from *Cassia auriculata* leaves docked against IFN-alpha resulted in receptor and ligand complex. The docked structures were analyzed and the interactions were seen. Hydrogen bond interactions and the binding distance between the donors and acceptors were measured for the best conformers (Archana *et al*., 2010). The Binding energy is correlated with the probability of affinity and stable bound between ligand and its receptor. Binding energy values may also predict the bioactivity value for a ligand to the corresponding receptor (Kartasasmita *et al*., 2009). The result of thisstudy shows that the docking of apigenin against IFN-alpha formed two hydrogen bonds each with the binding energy of–4.71 Kcal/mol and the Luteolin against IFN-alpha formed three hydrogen bonds each with the binding energy of -7.38 Kcal/mol respectively. The overall result summarized in table 5.

From the docking study it is evident that Luteolin has the ability to suppress or inhibit the activity of IFN-alpha when compared toapigenin (Luteolin have more interactions and least binding energy than the apigenin). Hence Luteolin may be considered as a strong inhibitor of IFN-alpha and would serve as a natural therapeutic agent against psoriasis.

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