JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

AN INSILICO EVALUATION OF ANTI INFLAMMATORY DRUGS -IN MULTIPLE SCLEROSIS

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ABSTRACT:

Inflammation has always been thought of as detrimental in the pathophysiology of multiple sclerosis (MS). However, emerging genetic data, magnetic-resonance-imaging studies, and immunopathological evidence challenge this simplistic view. The evidence leads to the conclusion that inflammation is tightly regulated, and that its net effect may be beneficial in MS, thus explaining some of the results from recent trials of anti-inflammatory agents. The use of anti-inflammatory drugs to treat MS may not be appropriate in all cases. Corticosteroids, such as oral prednisone and intravenous methylprednisolone, are prescribed to reduce nerve inflammation. In multiple sclerosis, an abnormal immune system attacks healthy nerve cells, causing inflammation and lesions in the brain and spine. The immune system primarily attacks myelin, a fatty substance that insulates nerve fibers (axons) and helps in the conduction of electrical signals.

Key words: methylprednisolone, dexamethasone and prednisone.

INTRODUCTION

Multiple sclerosis a chronic neuroinflammatory disease of the central nervous system characterized by neurodegeneration, demyelination, and astroglial proliferation, affecting both white and gray matter of neuronal cells. Clinically, MS is characterized by relapsing-remitting phenotypes and neuropathologic manifestations in which the patient experiences clinical attacks causing neurologic dysfunction including optic neuritis and transverse myelitis.[1]

Different ways of immunization and different animal species and strains mirror different aspects of the neuropathology of multiple sclerosis, such as inflammation, demyelination or axonal damage, and reflect different clinical courses. In all these models, the first immune reactions take place in lymph nodes from which immune cells migrate into the circulation and then to the central nervous system. Adoptive transfer of myelin-reactive T cells from these animals produces pathology and disease in the central nervous system of naïve healthy recipients. In the human disease, autoreactive T and B cells specific for a variety

of central antigens are present in the immune repertoire. These cells appear to be activated in the periphery through a number of mechanisms which causes them to home to the central nervous system. [2]

Inflammation is typically associated with relapses, and neurodegeneration with progression, it is now recognized that both pathologies are present in essentially all patients across the entire disease continuum. [3]

Nowadays new therapeutic drugs and stem cell therapy has advanced role in the treatment of MS. The long term use of current therapies is not treacherous and unsound. Herbal compounds, medicinal plants have anti-inflammatory, antioxidant and repairing myelin lead to inhibition of inflammation. MS is characterized by 2 pathological hallmarks: 1) inflammation with demyelination, and 2) astroglial proliferation (gliosis) and neurodegeneration. Tissue damage in MS is restricted to the central nervous system (CNS), sparing the peripheral nervous system. Clinically, MS can follow 2 paths: relapsing or progressive. Most commonly, onset is a relapsing form of MS (RMS), manifested as discrete episodes of neurological dysfunction followed by partial, complete, or no remission. Over time, relapses usually decrease in frequency but a gradual worsening often supervenes, resulting in uninterrupted progression (termed secondary progressive MS [SPMS]) [4]

The protein used used for docking studies is downloafde3d from PDB includes the 1hoy-acetyl choline esterase receptor.

MATERIALS AND METHODS

DOCKING

The interaction between the ligand and protein was determined by using Auto-docking via Pyrx virtual screening tool.[4]

- **Preparation of Ligand**
  The 3D structure of the compound was obtained from Pubchem, which contains information about the small molecule and their biological activities.
- **Preparation of Protein Protein**
  Proteins are the macromolecule contains one or more amino acid residues. The 3D structure of the protein was obtained from PDB (Protein data bank).
- **Conversion of ligand from SDF to PDB format**
  Openbabel-2.3.2/obgui.exe was used.
- **Protein preparation and molecular visualization**
  pyMOL is software used for the both purposes. pyMOL can produce high quality 3D images of proteins.

RESULTSAND DISCUSSION

There are many compounds with poor bioavailability shows less effective against disease. To solve this problem, predicting bioavailability properties will be great advantage for drug development. Hence using computer based methods like docking tools were studied. Increased hydrogen bond interaction and binding affinity score express the strong binding of constituents with the selected receptor.

Anti-inflammatory drug is the main category of drug used in the treatment of multiple sclerosis. By using insilico studies showed that Anti-inflammatory drugs has better affinity in their binding sites.Neurodegeneration in secondary progressive multiple sclerosis the main antecedent is oxidative stress and mitochondrial dysfunction .[6]

Table 1 shows the hydrogen bond interactions and binding affinity of constituents with receptor (1HOY).Table 1- 2 gives the physicochemical properties, pharmacokinetics and drug likeness properties of the drugs methylprednisolone, dexamethasone and prednisone.

Table 1: Physicochemical properties of methylprednisolone

Physicochemical Properties	**Methylprednisolone**
Formula	**$C_{22}H_{30}O_5$**
Molecular weight	**374.47 g/mol**
Num. heavy atoms	**27**
Num. arom. heavy atoms	**0**
Fraction Csp3	**0.73**
Num. rotatable bonds	**2**
Num. H-bond acceptors	**5**
Num H-bond donors	**3**
Molar Refractivity	**101.87**
TPSA	**94.83 Å²**

Table 2: Pharmacokinetics of Methylprednisolone

Pharmacokinetic Parameters	Methylprednisolone
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2, 2C9 inhibitor	No
Log K_p (skin permeation)	-7.20 cm/s

Table 3: Physicochemical properties of dexamethasone and prednisone

Physicochemical Properties	Dexamethasone	Prednisone
Formula	C22H29FO5	C21H26O5
Molecular weight	392.46 g/mol	358.43 g/mol
Num. heavy atoms	28	26
Num. arom. heavy atoms	0	0
Fraction Csp3	0.73	0.67
Num H-bond donars	3	2
Num H-bond acceptors	6	5
Molar Refractivity	101.96	96.10
TPSA	94.83 Å²	91.67 Å²

Table 4: Pharmacokinetics of Dexamethasone and Prednisone

Pharmacokinetic Parameters	Dexamethasone	Prednisone
GI absorption	High	High
BBB permeant	No	No
P-gp substrate	Yes	Yes
CYP1A2 inhibitor	No	No

CYP2C19	No	No
CYP2D6,3A4 inhibitor	No	No
Log K_p (skin permeation)	-7.32 cm/s	-7.45 cm/s

DOCKING IMAGES

Molecular docking

Molecular docking is used to recognize and optimize drug candidates by examining and modelling molecular interactions between ligand and target macromolecules. Molecular docking are used to generate multiple ligand conformations and orientations and the most appropriate ones are selected.

Figure 1: Docking image of Methylprednisolone

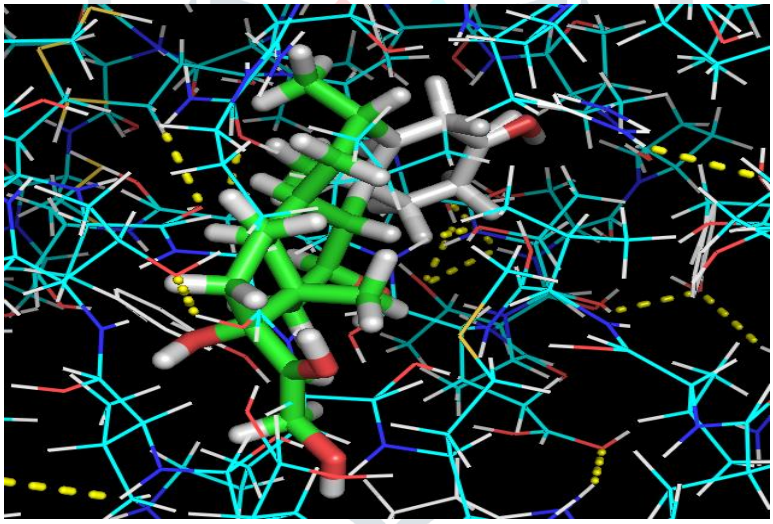


Figure 2: Docking image of Dexamethasone

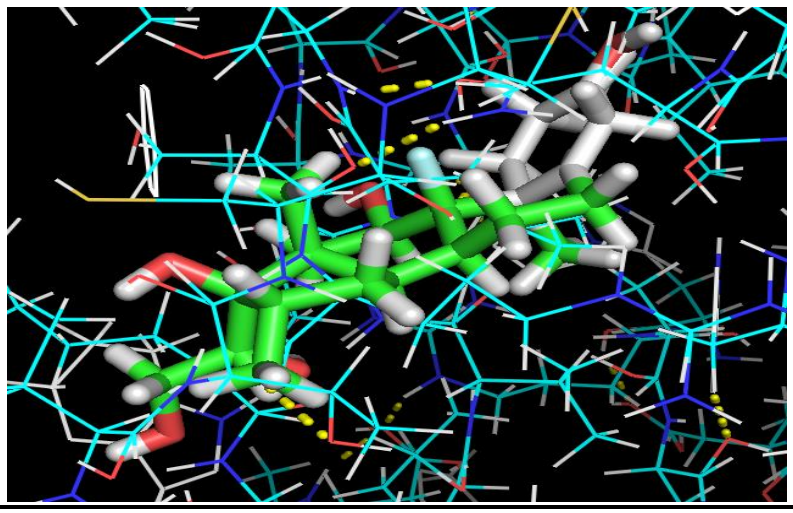
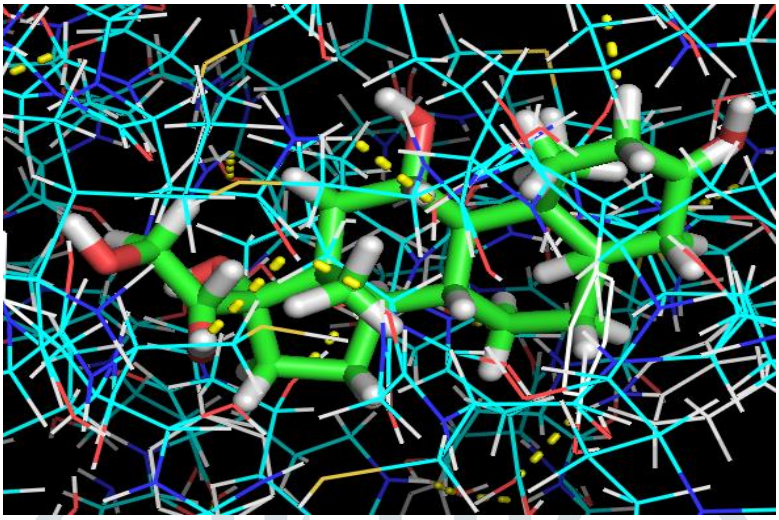


Figure 3: Docking image of Prednisone



DOCKING SCORE

Drugs	Docking Score (Kcal/Mol)	Hydrogen Bond
Methylprednisolone	**-7.1**	**5**
Dexamethasone	**-6.5**	**3**
Prednisone	**-6.4**	**4**

CONCLUSION

Computational tools may be helpful in finding the cause of this syndrome. Multiple sclerosis is becoming more widespread in today's scenario and their diversity is increasing at high pace thus an effective and efficient treatment is an urgent need of present times. The study shows that anti-inflammatory drugs are having best binding capacity with the 1HOY receptor. The binding affinity for i anti-inflammatory drugs with 1HOY receptor is also greater. Thus we can conclude that anti-inflammatory drugs can be used for the treatment of Multiple sclerosis.

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