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An *in silico* Evaluation of Immunomodulators-in Multiple Sclerosis

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Abstract:

Immune-modulating drugs mainly used as first line agent for multiple sclerosis due to their high safety profile. Different therapeutic strategies are available for treatment of multiple sclerosis (MS) including Immunosuppressants, Immunomodulators, and monoclonal antibodiesfebuxostat, a xanthine oxidase inhibitor, ameliorated both relapsing-remitting and secondary progressive experimental autoimmune encephalomyelitispreventing neurodegeneration.Febuxostat is a non-purine selective xanthine oxidase (XO) inhibitor that is currently used for the treatment of gout. febuxostat decreases XO-mediated ROS production and improves mitochondrial function. febuxostat antecedently showed that treatment of ameliorated relapsing-remitting and secondary progressive subclasses of murine experimental autoimmune encephalomyelitis (EAE) by inhibiting the over production of ROS and reducing neurodegeneration.

Key words: Febuxostat, Probencid, Sulfinpyrazone, Docking, anti-inflammatory.

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]

There is no single drug for multiple sclerosis. The management and slowing the progression of pathosis is the main aim of immunomodulating drugs. There are a spectrum of therapeutic strategies and specific agents for treatment of multiple sclerosis (MS). While immune-modulating drugs remain the first-line agents for MS predominantly due to their benign safety profile.[2] One concept of these novel drugs is to hamper migration of immune cells towards the affected central nervous system (CNS).

Fingolimod is the first oral drug approved for MS.Inhibtion of egress of lymphocytes from lymph nodes is the main action of fingolimod and the prevention of inflammatory CNS foray by blocking adhesion molecule by the monoclonal antibody Natalizumab.The second approach is using highly specific monoclonal antibodies such as alemtuzumab (anti-CD52) or rituximab/ocrelizumab (anti-CD20) for the dcepletion of T and B cells. Execution of inflammation in the nervous system is partially understood. An increased risk in patients include cardiac problems, depression, reduction of blood cells, allergic reactions and also leads to drug induced auto-immune disorders.[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.

MATERIALS AND METHODS

DOCKING

The interaction between the ligand and protein was determined by using Auto-dock vina 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.

RESULTS AND 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.

Immunomodulators and monoclonal antibodies is the main category of drug used in the treatment of multiple sclerosis. By using insilico studies showed that immunomodulating 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 (2Z64).Table 1- 2 gives the physicochemical properties, pharmacokinetics and drug likeness properties of the drugs febuxostat, probencid and sulfinpyrazone.

Table 1: Physicochemical properties of febuxostat

Physicochemical Properties	Febuxostat
Formula	C16H16N2O3S
Molecular weight	316.37 g/mol
Num. heavy atoms	22
Num. arom. heavy atoms	11
Fraction Csp3	0.31
Num. rotatable bonds	5
Num. H-bond acceptors	5
Num H-bond donors	1
Molar Refractivity	85.10
TPSA	111.45 Å²

Table 2: Pharmacokinetics of febuxostat

Pharmacokinetic Parameters	Febuxostat
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2, 2C9 inhibitor	Yes
Log K_p (skin permeation)	-5.46 cm/s

Table 3: Physicochemical properties of Probencid and Sulfinpyrazone

Physicochemical Properties	Probencid	Sulfinpyrazone
Formula	C13H19NO4S	C23H20N2O3S
Molecular weight	285.36 g/mol	404.48 g/mol
Num. heavy atoms	19	29
Num. arom. heavy atoms	6	18
Fraction Csp3	0.46	0.13
Num H-bond donars	1	0
Num H-bond acceptors	5	3
Molar Refractivity	73.43	120.08
TPSA	83.06 Å²	76.90 Å²

Table 4: Pharmacokinetics of Probencid and Sullfapyrazone

Pharmacokinetic Parameters	Probencid	Sulfinpyrazone
GI absorption	High	High
BBB permeant	No	Yes
P-gp substrate	No	No
CYP1A2 inhibitor	No	No
CYP2C19	Yes	Yes
CYP2D6,3A4 inhibitor	No	Yes
Log K_p (skin permeation)	-5.76 cm/s	-7.13 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 febuxostat

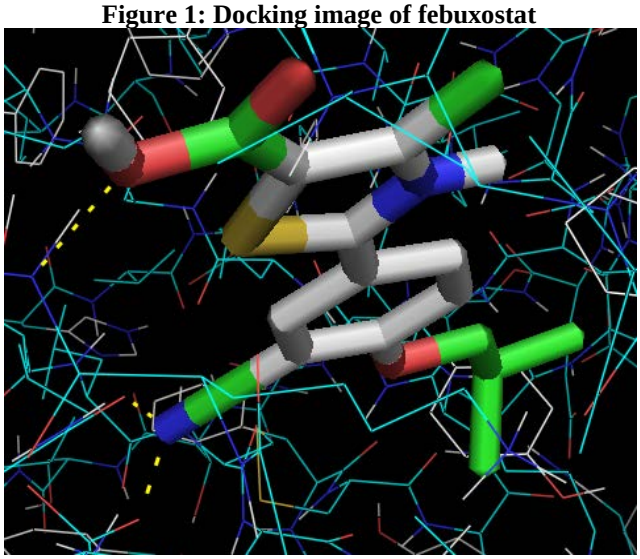


Figure 2: Docking image of Probencid

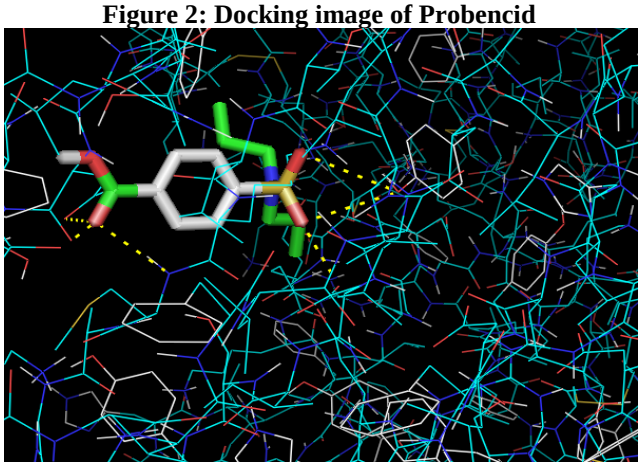
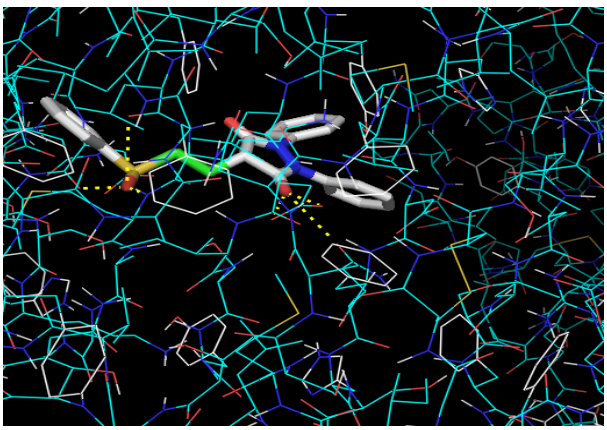


Figure 3: Docking image of Sulfinpyrazone



DOCKING SCORE

DRUGS	DOCKING SCORE (kcal/mol)	HYDROGEN BOND
Febuxostat	-7.6	3
Probencid	-6.5	6
Sulfinpyrazone	-9.2	6

CONCLUSION

Computational tools may be helpful in finding the cause of this syndrome. Multiple sclerosis 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 immunomodulators is having best binding capacity with the 2Z64receptor.The binding affinity for immunomodulators with 2Z64 receptor is also greater. Thus we can conclude that immunomodulators can be used for the treatment of Multiple sclerosis.

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