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Molecular dynamic properties and Insilico screening of neuroprotective activity of *Clitoria ternatea* against Glutamate receptors

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ABSTRACT

Multiple sclerosis is a popular autoimmune disease attack mainly the Central nervous system. It attacks the age group of people from 20-50, mostly women are attacked than men. During multiple sclerosis, demyelination takes place along with axon damage and paralytic effect. Various symptoms of multiple sclerosis include muscle weakness, weak reflexes, muscle spasm, movement difficulty. Moreover, treatment of multiple sclerosis vai drugs includes various side effects. Medicinal plants possess many phytochemicals of greater therapeutic value and many of the possess effective to treat multiple sclerosis, Chemical constituents exhibit its effect over multiple sclerosis by inhibiting many proteins involved in demyelination. Molecular docking is a computational design approach which facilitates the best molecule from a group which may bind with the highest affinity with the intended target by providing a biological system. This process enables on the basis of the specific algorithm and involves a scoring function in order to rank molecules that fit the target. The study has been made to investigate the potential of phytochemicals from clitoria ternatea -inositol and quercetin as inhibitors of glutamate receptors. Drug likeness property determined based on molinspiration.com. The affinities of those selected chemical constituents over various glutamate receptor were studied for scoring function. Receptors with PDB code 1EQ8,4E0W,3KR2 were chosen to dock against the chemical constituent Inositol richest chemical constituent in Clitoria ternatea and scoring function was found to be -3.45,-4.56, -5.67kcal/mol.

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INTRODUCTION

Multiple sclerosis is an autoimmune disease that mainly occurs in young adults. The physiology of disease is not understood well; it has genetic and environmental factors which has an important role in disease intiation and progression. Main symptoms of multiple sclerosis are acute inflammation associated with demyelination and other one is an axonal loss (Camiña-Tato *et al.*, 2010). After cell injury oligodendrocytes precursor, which are residing at parenchyma cells release myelinating oliogodendrocyte. Use of complementary and alternative medicine in particular herbal remedies has risen role in treating multiple sclerosis. Herbal therapy

has been used as a healthy strategy for the treatment of many diseases. Medicinal plants have a potential therapeutic effect in treating several disorders such as anticancer, diabetic, neurodegenerative disorders. Clitoria ternatia is a perennial herb also known as butterfly pea has a significant interest based on its potential medicinal application which as a broad application from nitrogen-fixing to cosmetic, food colouring, a source of insecticide and traditional medicine (Bowling, 2018). Plants are having numerous medicinal properties and acting as good alternative sources to treat for existing noncommunicable diseases worldwide (Jiang *et al.*, 2001).

Further, numerous research focused that foods having rich source in antioxidants play a pivotal role in the prevention and management of a range of oxidative stress associated with chronic diseases (Nave and Trapp, 2008).The mechanisms of antioxidants in to control oxidative stress in enzyme system are diverse, which included scavenging of free radicals, inhibition of oxidative enzymes, chelation of metal ions, and acting as antioxidant enzyme cofactors (Nave, 2010; Mitsikostas and Goodin, 2017). Therefore, diets rich in antioxidants could be a better alternative source to manage neurodegenerative and its chemical constituent inositol has been performed for insilico screening studies (Shende *et al.*, 2012; Pati and Patil, 2011).

MATERIALS AND METHODS

Preparation of Target Receptors

Central nervous system receptor-like glutamate receptors were chosen for docking studies to treat MS. The crystal structure of the protein was isolated from the Protein Data Bank (PDB)(http://www.rcsb.org/pdb)for docking studies. The PDB codes for the chosen crystal receptors were1EQ8,4E0W,3KG2, as shown in Figure 3a, Figure 3b, Figure 3c.

Ligand Preparation

The higher content of chemical constituent, namely Inositol from Clitoria ternatea and the structure of the chemical constituents has been extracted from Universal PubChem structural database. The ligand molecule was cleaned for geometry and prepared for docking study saved as MOL file (Jain *et al.*, 2003; Mahad *et al.*, 2003).

RESULTS AND DISCUSSION

The active chemical constituents many medicinal herbs constituted compounds like inositol was treated for central nervous system diseases such as multiple sclerosis. The Ionositol Figure 1 was selected as ligand and docked against glutamate receptors. The ionositol was submitted in the w ww. molinspiration .com using Acs chem sketch structure drawer. The drug likeliness and molecular properties are shown in Figure 3a. The molecular properties such as molecular formula-C6H12O6, molecular weight174.11-, a number of Hydrogen bond-1, molecular log polarity molecular solubility -0.33, molecular polar surface area- 121.37, molecular volume 132.15and no stereo centers. The drug likeliness score was found to be -0.60, as shown in Figure 2. The transport and recognition of drugs is essential for target-specific therapy. The target-specific drug action can be assessed by the parameters such as Glutamate receptor described in Figure 3a, Figure 3b, Figure 3c.

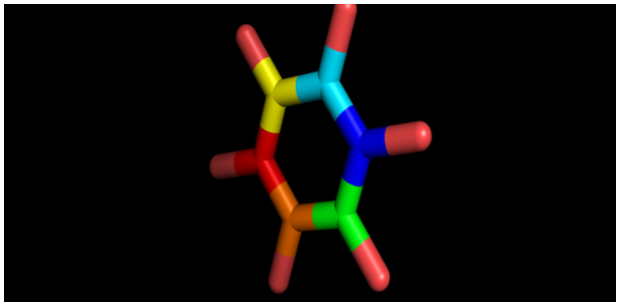
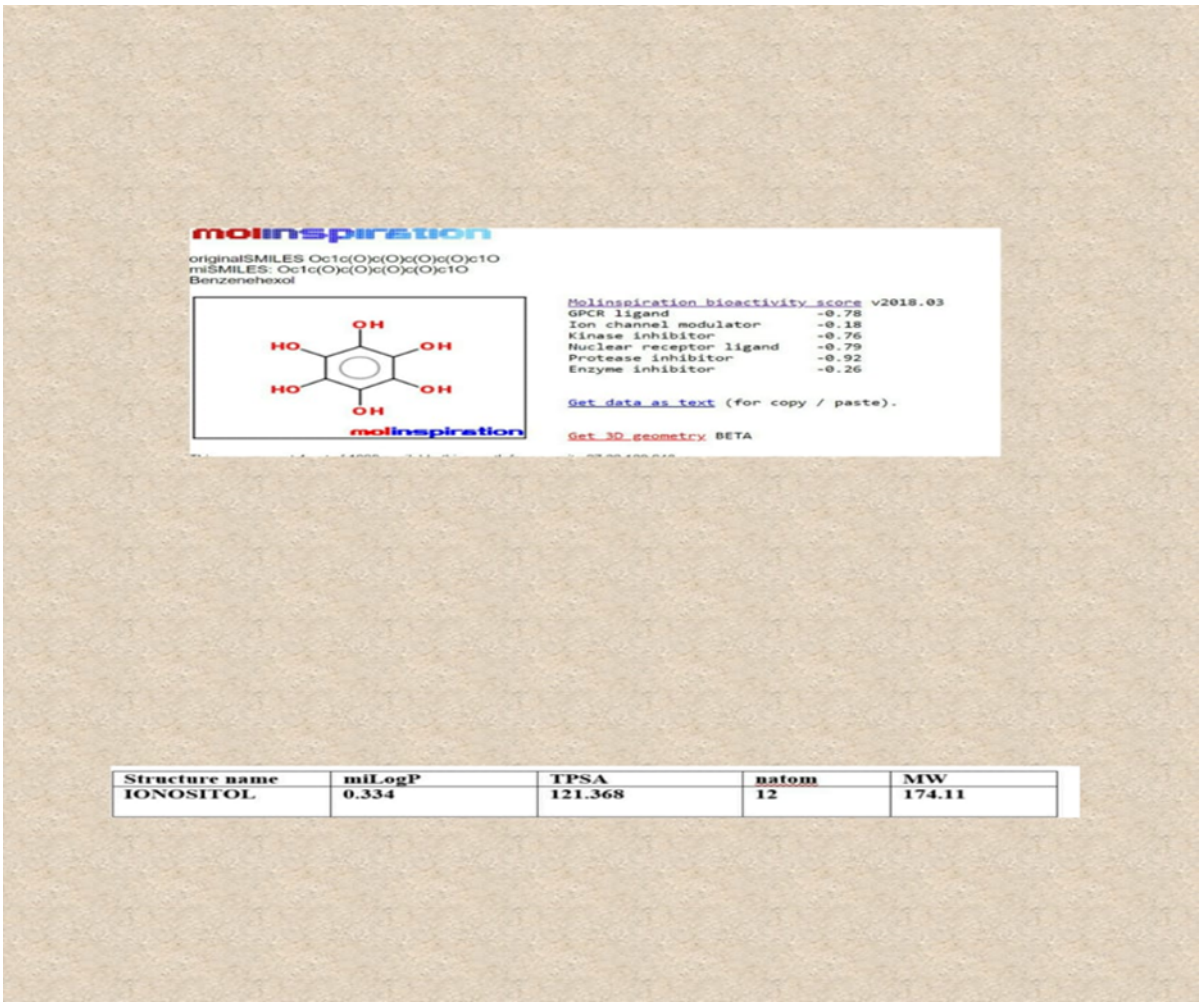


Figure 1: Three-dimensional structure of Ionositol

The target binding of the drug is essential for identifying the target site for therapeutic importance. The target-specific drug action cab is assessed by the parameters such as G-protein coupled, ion channel modulator, nuclear receptor and protease inhibitor. The bioactivity score of the compound was found to be GPCR ligand -0.78, Ion channel modulator -0.18, Kinase inhibitor-0.76, Nuclear receptor-ligand-0.79, Protease inhibitor-0.92, Enzyme inhibitor -0.26as shown in figure 2.the Insilco screening of inositol with glutamate receptors 1EQ8,4EOW,3KG2 were presented in the Figure 4 a,b,c. The procedure of docked compounds and their scoring function was identified by using pymol viewer and the docking score profile were tabulated as shown in Table 1. The active site of glutamate receptors was predicted by active site residues of glutamate receptors by CASTp Computed Atlas of Surface Topography of Proteins. The active sites residues of the metabotropic glutamate receptors were predicted by active site prediction tool. The active residues were 1EQ8-Thy,4EOW-Arg,3KG2-Glu as bioactive site Prediction: Active site recognization of glutamate receptor.

Active Site Prediction



Structure name	miLogP	TPSA	natom	MW
IONOSITOL	0.334	121.368	12	174.11

Figure 2: Biologically active score prediction of Ionositol

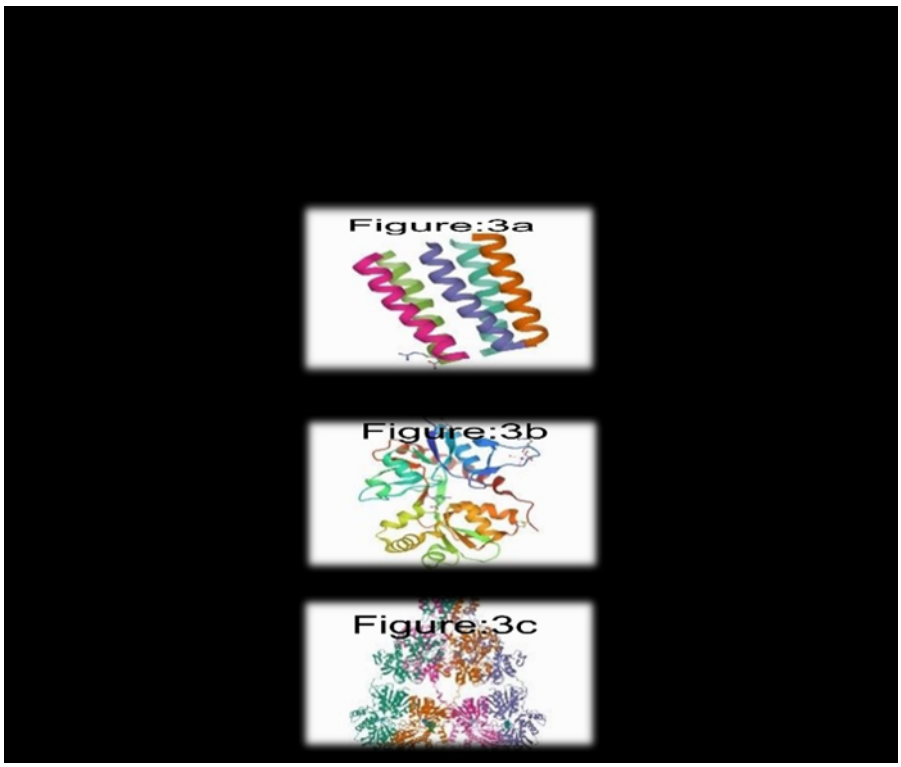


Figure 3: Three dimensional images of CNS acting receptors

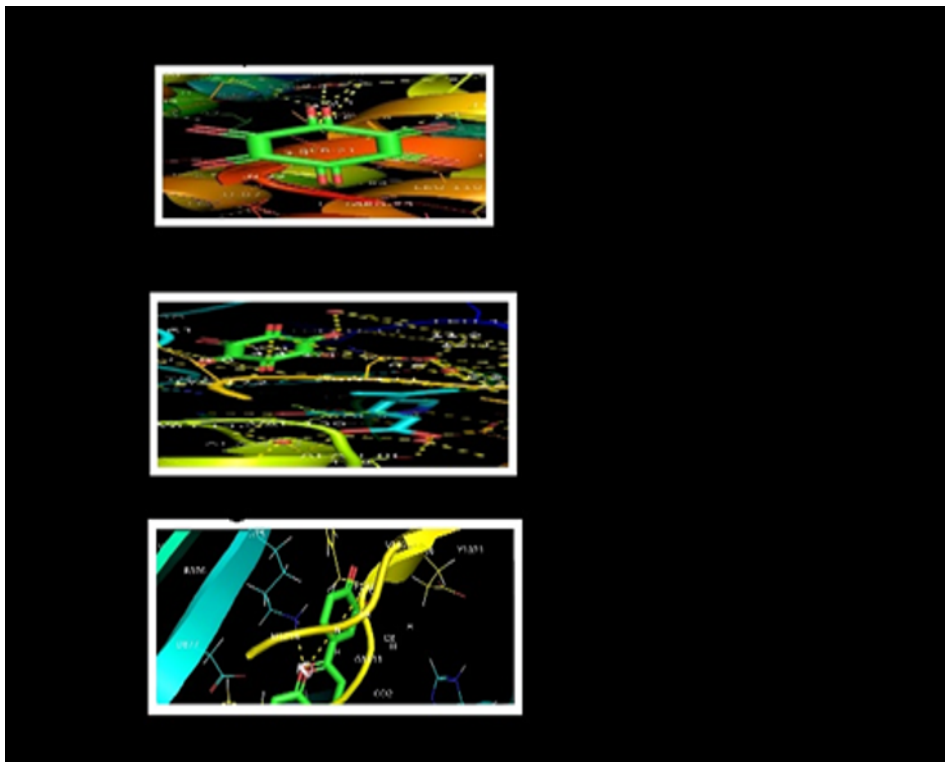


Figure 4: Molecular interaction of Ionositol with glutamate receptors

Table 1: Active Site prediction of Glutamate Receptors

Sl.No	Glutamate receptors	Active amino acid residues
1	1EQ8	Arg 206, Phe 208 6 2E4Z Pro 56, Gly-58, Lys-
2	4EOW	,Lys-71,Asn 74,Ser-159,Ser-229
3	3KG2	Tyr-236, Asp-318,319

Table 2: Molecular Interaction and Docking scores of Ionositol–Glutamate receptors

Sl.No	Ionositol with glutamate receptors	Score kcal/mol	Area	Atomic contact energy	Ligand transformation
1	1EQ8	-3.99557 kcal/mol	24.127624	101	3.75507, -7.71813, 106.414
2	4EOW	-4.07082 kcal/mol	13.926089	20	-12.9591, 28.9774, -26.7814
3	3KG2	-3.90899 kcal/mol	10.043383	150	-7.5, -7.5, -7.5

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Active site recoganization of glutamate receptors proof of human estrogen receptor The catalytic sites of Metabotrphic glutamate receptors area and volume of binding pocket was done with Computed Atlas of Surface Topography of Proteins (Castp) program (http://cast.engr.uic.edu)11.

Molecular docking

In the present study, the glutamate receptor proteins are docked with the eugenol ligand. The molecular docking was performed with AutoDock 4.2.1. In order to analyze the effect of ligand association, all the water molecules and the hetero atoms have been removed from the target protein. All the hydrogen atoms were added to the protein as it is required for the electrostatics and then non-polar hydrogen atoms were merged.

The predicted catalytic active sites of nearly 10 glutamate receptors were utilised as the agonist for active compound ionositol were characterised utilised for insilico docking binding studies which were presented in the Table 1. The docking score indicates the binding site deposit of target receptor and ionostiol ligand, as shown in Table 2. Ionositol has found more attraction over receptors such as1EQ8,4EOW,3KG2. The contact energy of the atoms, ligand via transformation and docking frequency was found to have the score such as -3.94kcal/mol,-4.96kcal/mol,-5.67kcal/mol. Further, the results have concluded to be valuable proof and improvement for new preventive and remedial medication against central nervous system disorders.

CONCLUSIONS

The potent lead molecule from medicinal herb *Clitoria ternatea* were selected and their interaction between receptor and ligand has ben studied by virtual screening techniques.As per the present study, we conclude that the Ionositol ligand was selected for docking study, which showed that very efficient interaction and exclusive inhibitory impact with receptor targets of nervous disorders through different glutamate receptors. Based on the study, all the three receptors 1EQ8,4EOW,3KG2 showed potent inhibitory activity by inositol lead moiety. Hence the presence research paper concluded that Ionositol can be strongly advised and prompted as a potent therapeutic agent for neurodegenerative disorders.

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The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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