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Research Article

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Comparative molecular docking study of rutin against GABA A type receptor and 4-aminobutyrate-aminotransferase for anti-convulsant activity

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ABSTARCT

Recently many chemical drugs are capable of causing the side effects to the humans; in order to prevent these side effects herbal based drugs is necessary for the better alternative. Epilepsy is the one of the neurological diseases caused by abnormalities in brain function nearly 50 million people were affected by this disease in entire world. Hence in this current study two different drug targets such as GABA type A receptor and 4-aminobutyrate-aminotransferase were docked with the natural isolated chemical structure Rutin and also compared the efficacy of the binding in between them and found that GABA type A receptor with negative binding energy of -2.68 kcal/mol is more stable than that of 4-aminobutyrate-aminotransferase with positive binding energy of +123.47 kcal/mol. Thus rutin shows more favorable binding to GABA type A receptor, so in future instead of the chemical drugs rutin can be used as drug candidate for epilepsy treatment.

Key words: Epilepsy, Abnormalities, Drug targets, Rutin, Docked.

INTRODUCTION

Neurological disorders are caused by improper function of nerve cells, biochemical, structural and electrical abnormalities in the nerves, brain, and spinal cord can result in a various range of symptoms[1-2]. Epilepsy is one of the most common long term serious neurological disorders [3].Convulsants are also known as epilepsy, nearly 50 million people in worldwide were affected by Epilepsy, and in developing world 80 % of them were affected by this disease[4], It is one of the most common neurological disorders. It was estimated that more than 10 million person with Epilepsy [5]. Seizures are characterized by a brief period of uncontrolled involuntary shaking. They may be generalized in the entire body or partial, involving only in the certain part of the body and they may be accompanied by loss of consciousness, brain injury, brain cancer, and stroke [6-7].

Herbal medicines are finished, labeled medicinal products that contain as active ingredients, aerial or underground part of plants or other plant materials, or combination thereof, whether in the crude state or as plant preparations. Medicines containing plant materials combined with chemically defined active substances, including chemically isolated constituents of plants are not considered to be herbal medicines [8]. Herbal preparations are most often recommended to treat epilepsy in Asian or African folk medicine practices. The herbs such as violet tree, bo tree, false pepper, kava, passion flowers and valerian were used for the seizures treatment.

In this current study the rutin compound was isolated from the natural source and analyzed for two different types of drug targets of convulsants. GABA receptors are active receptors that respond to the neuron transmitter gamma-

aminobutyric acid, GABA type A receptor is ligand gated ion receptor or ionotropic receptors responses by ligand binding and allows the chemical ions to pass through the membrane is one of the important drug target receptor for anti-epilepsy activity [9-14].4-aminobutyrate-aminotransferase is another drug target enzyme was chosen in this study to compare binding energy of rutin with GABA type A receptor.

EXPERIMENTAL SECTION

Retrieval of the natural compound

The chemical structure rutin of pubchem id (CID 5280805) was retrieved from pubchem (http://pubchem.ncbi.nlm.nih.gov/) of molecular formula $C_{27}H_{30}O_{16}$ and Molecular Weight is 610.5175, other name of this compounds are rutoside, Birutan, Sophorin, Eldrin, Venoruton, Rutin trihydrate, Quercetin 3-rutinoside, Bioflavonoid, Myrticolorin respectively. Canonical SMILES of this compound was taken as input to calculate the general molecular properties.

Drug likeness screening and Optimization of the structures

Drug likeness using the computational tools is the qualitative method of screening the lead molecules before proceeding to in-vitro and in-vivo studies. Molecular properties were calculated using molinspiration online tool, (http://www.molinspiration.com/) properties are important for biological process. A lop P, Molecular weight, hydrogen bond donors (HBD) and hydrogen bond acceptors(HBA) important drug likeness property of Lipinski's rule of 5[15] and molecular properties of veber [16] like TPSA(Total polar surface area) , no of rotatable bonds(nrotb)and volume are important property for drug transportation in invivo system. Theoretical method of screening chemical structures for drug likeness property were optimized using the GROMOS96 force filed, to prevent from imbalance of valence electrons and non bonded interactions respectively.

Drug target identification and retrieval

The drug target proteins for convulsants, Insilco studies was proceeded with two different types of drug targets such as 4-aminobutyrate-aminotransferase enzyme bound with gamma-ethynyl gaba of id 1OHY and its X-ray crystallographic structure with 2.80Å resolution with UniProtKB unique identification number is P80147 with amino acid sequence of 472 length and GABA type A receptor bound with binding epitope on calreticulin of id 3DOW and its X-ray crystallographic structure with 2.30Å resolution with UniProtKB unique identification number is O95166 with amino acid sequence of 119 length was retrieved from PDB database. (http://www.rcsb.org/pdb/home/home.do).

Preparation of protein

The drug target protein from protein databank was downloaded and prepared for receptor ligand interaction studies before that hetatoms bound to the protein was removed, subsequently water molecules also removed and proceed for energy minimization to remove the bad steric clashes using GROMOS96 force filed available through swisspdb deep view project4.01.

Molecular docking

The different drug targets were docked with one natural isolated ligand rutin and interaction between ligand and protein active site was theoretically analyzed using the computational tools and software's. In this study Molecular docking was performed using the structure based drug designing concept with autodock 4.01v.

RESULTS AND DISCUSSION

Chemical properties of ligand are important for the biological properties like bioavailability, bio efficacy and transportation, any change in drug likeness will change the ligand biological model, but for natural isolated products, secondary metabolites, bioactive compounds form microorganism, fungi and plants will violate the rules in many cases. Perhaps they will have bioactivity and safe rather than chemical drugs. The properties of natural compound rutin (Table 1).

Stability of the protein

Stability is important for proteins, the drug targets GABA type A receptor and 4-aminobutyrate-aminotransferase were initially calculated using the Swiss Pdb deep view project 4.01v software. But few amino acids shows positive energy before energy minimization to stabilize the protein energy, force filed GROMOS96 was applied for both the

proteins and the energy is calculated and shown in the table 2. The drug targets after applying force filed is shown in the figure 1 and figure 2.

Table 1: Molecular properties of Rutin

Molecular Composition	C: 0.531, H: 0.050, O: 0.419
miLogP	-1.063
TPSA	269.427
No of atoms	43.0
MW	610.521
nON (HBA)	16
nOHNH (HBD)	10
No of violations	3
No of rotatable bonds	6
volume	496.068

Table 2: Drug targets energy

Drug targets	Before energy minimization KJ/mol	After energy minimization KJ/mol
GABA type A receptor	-3661.654	-5834.424
4-aminobutyrate-amino transferase	-16301.493	-24372.740

Figure 1: Drug target 4-aminobutyrate-aminotransferase applied with force filed

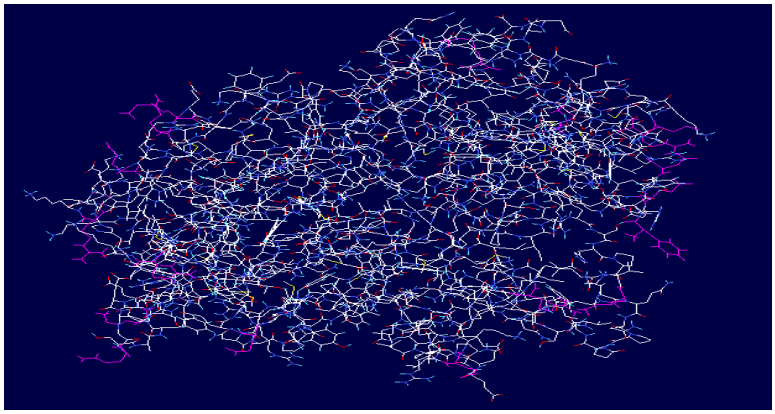
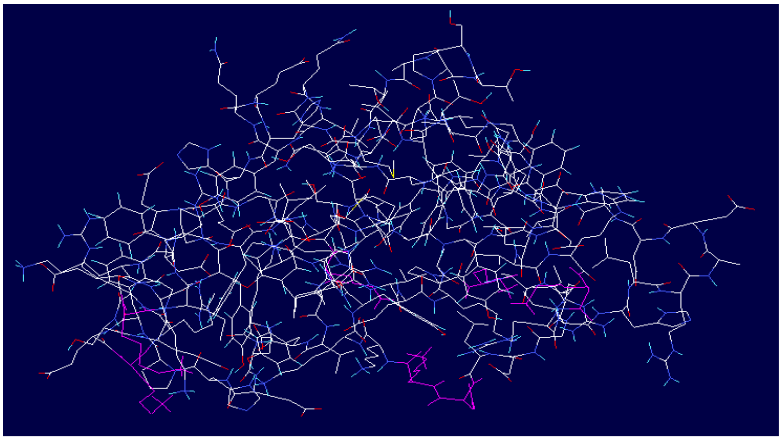


Figure 2: Drug target GABA type A receptor applied with force filed



Receptor ligand interaction

The crucial amino acid in active site were defined as flexible residues in auto dock 4.01v with grid spacing of 0.5 (X), 0.5 (Y), 0.5 (Z) in 3D direction respectively with 0.4Å grid resolution. Initially auto gird option was performed

followed by auto dock flexible docking using genetic algorithm for two drug targets and the active site of the each protein was obtained from the PBDSUM database (https://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum /GetPage.pl).GABA type A receptor with active site amino acid residues of Glu19,Arg30,Lys50,Leu52 and 4-aminobutyrate -aminotransferase with active site amino acid residues of Gly136,Ser137,Arg192,Gln301, Lys329 respectively. The results after docking was visualized using the acclerys discovery studio 3.5 visualizer in 2D representation, various energy parameters of docking for GABA type A receptor(figure 3) and 4-aminobutyrate-amino transferase (figure 4) is tabulated in the table 3 and interaction is stated in the table 4 and table 5.

Figure 3: GABA type A receptor binding with active site residues

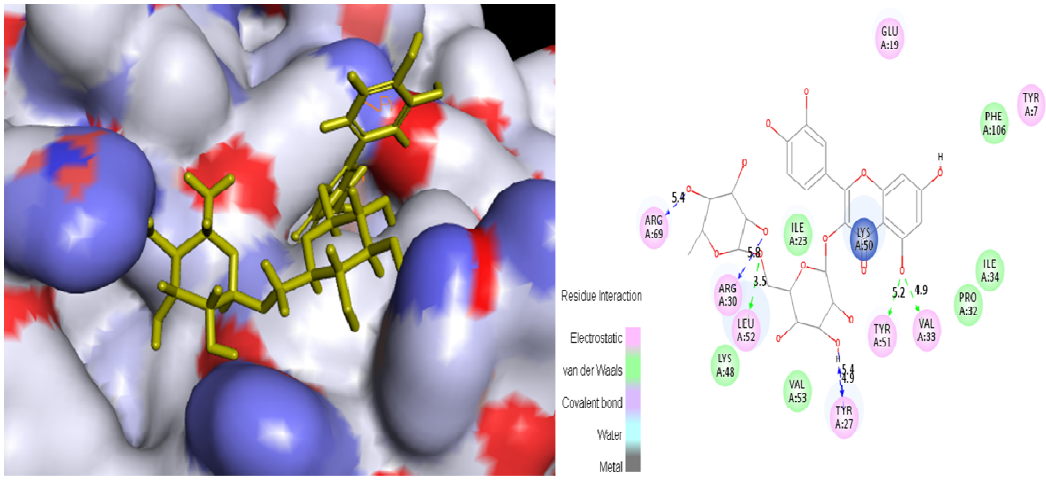


Figure 4: 4-aminobutyrate-aminotransferase binding with active site residues

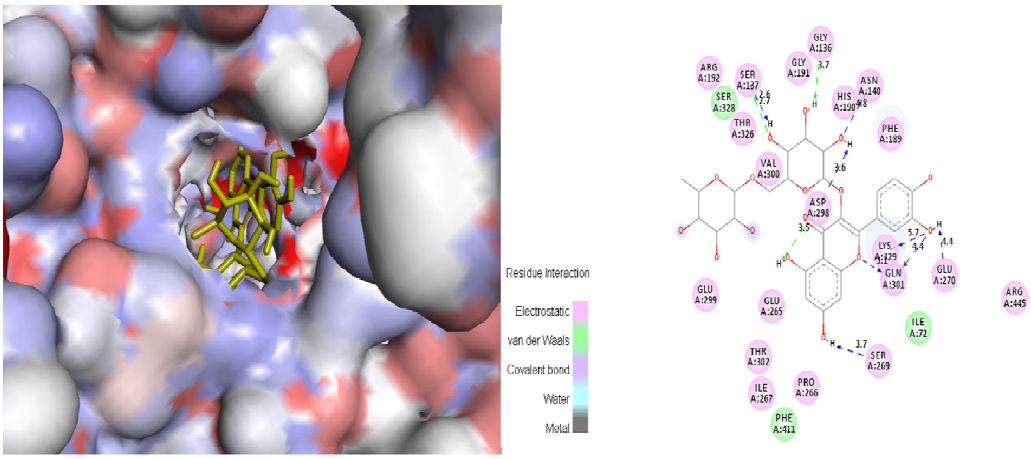


Table 3: Various energy parameters of docking

Parameters	GABA type A receptor	4-aminobutyrate-amino transferase
Estimated Inhibition Constant, Ki	10.93 mM	145.95 mM
Estimated Free Energy of Binding	-2.68 kcal/mol	+123.47 kcal/mol
Final Intermolecular Energy	-1.68 kcal/mol	+101.84 kcal/mol
vdW + Hbond + desolv Energy	-1.60 kcal/mol	+101.98 kcal/mol
Electrostatic Energy	-0.08 kcal/mol	-0.14 kcal/mol
Final Total Internal Energy	-5.39 kcal/mol	+17.24 kcal/mol
Torsional Free Energy	+4.39 kcal/mol	+4.39 kcal/mol
Unbound System's Energy	+0.00 kcal/mol	+0.00 kcal/mol

Table 4: The below mentioned table is the binding energy of ligand to the active site/binding site of the GABA A type receptor with Rutin

RECEPTOR and LIGAND	Amnioacid Binding	Distance in Å	Binding energy kcal/mol
GABA TYPE A RECEPTOR WITH RUTIN	Arg69	5.4	-2.68
	Arg30	5.8	
	Leu52	3.5	
	Tyr 27	4.9,5.4	
	Tyr51	5.2	
	Val33	4.9	

Table 5: The below mentioned table is the binding energy of ligand to the active site/binding site of the 4-aminobutyrate-aminotransferase with Rutin

RECEPTOR and LIGAND	Amnioacid Binding	Distance in Å	Binding energy kcal/mol
4-AMINOBUTYRATE-AMINOTRANSFERASE WITH RUTIN	Gly136	3.7	+123.47
	Ser137	2.7,2.6	
	Asn140	4.8	
	Asp298	3.6,3.5	
	Ser269	3.7	
	Glu270	4.4	
	Lys329	5.7	
	Gln301	4.4	

CONCLUSION

Nowadays importance of the herbal based medicine research is going on all over the entire world for the better medicine to cure the dreadful diseases without side effects .The active metabolites from various natural sources of microbes, plants, animal and marine were used a potent chemical drugs alternatives. Many pharmaceutical companies were investing the millions of dollar in the natural drug production in large quantity with fewer prices to reach the people. Thus from this current study the Rutin shows more potent to bind with the GABA type A receptor with negative binding energy of -2.68 kcal/mol when compared with 4-aminobutyrate-aminotransferase with positive binding energy of +123.47 kcal/mol .Hence in future the rutin can be used a drug candidate for the treating the epilepsy specifically of GABA A type receptor.

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