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Article

In silico investigation on the probable macromolecular drug targets involved in the anti-schizophrenia activity of *Nardostachys jatamansi*

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Existing medications i.e. the antipsychotic drugs are known to be effective in treating only the positive symptoms of schizophrenia, while being ineffective on negative and cognitive symptoms of the disease. In addition, these medications cause extrapyramidal symptoms, forcing many patients towards natural medicine in the hope of minimising the unwanted adverse effects. *Nardostachys jatamansi* is a medicinal plant that has been traditionally prescribed for various types of brain disorders. The active constituents of the plant have beneficial effects on the negative and cognitive symptoms of schizophrenia. This study was designed to identify the active constituents of *Nardostachys jatamansi* with the highest binding affinities for the key macromolecular drug targets involved in the pathophysiology of schizophrenia and thereby elucidate the possible mechanism of action. These targets are dopamine receptors, Gamma-aminobutyric acid receptors, N-methyl-D-aspartate receptors and Phosphodiesterase 10A. The results of molecular docking showed that, β-sitosterol, chlorogenic acid, oleanic acid and ursolic acid, displayed high binding affinity toward all the macromolecular drug targets. Ligands with steroid backbone and pentacyclic triterpene structure have been found to possess high binding affinity toward the dopamine receptor and phosphodiesterase 10A. While ligands with carbonyl group form stronger binding interactions with the N-methyl-D-aspartate receptor.

KEYWORDS: Schizophrenia. *Nardostachys jatamansi*. Dopamine. GABA. NMDA.

INTRODUCTION

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. It is a prototype of a category of mental illness called psychosis. And psychosis refers to some specific abnormalities of cognition and often characteristically abnormal perceptions of reality. The symptoms of schizophrenia can be classified into three categories, which are positive symptoms like hallucination and delusion, negative symptoms like social isolation and lack of emotion and cognitive symptoms like thinking problems and reduced attention (Andreasen, 1982; Andreasen *et al*., 1995; Crow, 1981). It has been suggested that schizophrenia should be classified as a cognitive disorder instead of being known as a psychotic disorder as the negative and cognitive symptoms precede the psychotic symptoms.

The antipsychotic drugs are known to be the best available pharmacological treatment for schizophrenia so far. They are categorised as typical antipsychotics (e.g. haloperidol and chlorpromazine) and atypical antipsychotics (e.g. risperidone and olanzapine). These medications were proved to be effective in alleviating the positive symptoms of schizophrenia. However, they have not been effective in treating the negative and cognitive symptoms of the disease (Kahn, Keefe, 2013). In addition, these medications cause undesired side effects i.e. extrapyramidal symptoms, weight gain and sexual dysfunction (Hoenders *et al*., 2018). Thus, many schizophrenic patients prefer to use nonconventional

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treatment or medications in the hope of minimising the unwanted adverse effects. Nonconventional treatment includes alternative and complementary medicine and therapeutic lifestyle changes (Hazra *et al.*, 2010). Natural medicine is a part of complementary medicine that based on utilizing natural drugs produced by living organisms i.e. animal and plant instead of the synthetic drugs i.e. chemical agents (Hoenders *et al.*, 2018).

Nardostachys Jatamansi (NJ) which belongs to the Valerianaceae family is an important medicinal plant indigenous to India. It grows in the eastern Himalayas in Nepal, Bhutan, Myanmar and southwest China. The plant is commonly known as balchar or spikenard. It has been prescribed in Ayurvedic medicine since 800 B.C. for various type of ailments such as hysteria, cholera, palpitations, epilepsy and similar convulsive disorders. The roots and the rhizome extracts of the plant have been studied for other activities such as antianxiety, hepatoprotective, antiparkinson, and antidepressant (Pandey *et al.*, 2013). Moreover, some studies have pointed to the beneficial effects of the active constituents of the plant on the negative and cognitive symptoms of schizophrenia (Purnima, Kothiyal, 2015).

Therefore, this study has been conducted to study the binding affinities of the active constituents of NJ to the main macromolecular drug targets involved in the pathophysiology of schizophrenia. In which, molecular docking study has been performed to illustrate the binding interactions between the active constituents of NJ and the binding site residues of the macromolecular drug targets.

MATERIAL AND METHODS

Selection of phytochemicals from *Nardostachys jatamansi*

First, the chemical constituents presented in NJ were listed (Kim *et al.*, 2015). These chemical constituents were filtered based on their biological activities that have been reported in the scientific literature. Then, the constituents were further filtered based on Lipinski's rule of five to ensure that only constituents with drug-like properties are refined. According to this rule, the orally absorbed drug should have a molecular weight (Mwt) ≤ 500 Dalton, partition coefficient (logP) ≤ 5, number of hydrogen bond donor ≤ 5, and number of hydrogen bond acceptor ≤ 10. Additionally, the CNS active drugs should have a number of rotatable bonds < 8 and polar surface area (PSA) < 90 Å^2. Only constituents which fulfil at least 3 of these criteria were involved in the present study (Table I).

TABLE I - Inclusion criteria for CNS penetration properties (Banks, 2009; Mikitsh, Chacko, 2014; Pajouhesh, Lenz, 2005)

Property	Inclusion criteria
Molecular weight (MW)	≤ 500 Dalton (g/mol)
Partition coefficient (logP)	≤ 5
Number of H-bond donor	≤ 5
Number of H-bond acceptor	≤ 10
Number of rotatable bonds	< 8
Polar surface area	20 - 90 Å^2
Formal charge	0

Protein preparation

The three-dimensional (3D) structures of the macromolecular drug targets, dopamine (D2), N-methyl-D-aspartate (NMDA), gamma-aminobutyric acid (GABAA), and phosphodiesterase (PDE) 10A, were selected and downloaded from Protein Data Bank (PDB) (Table II). Biovia Discovery Studio (DS) and AutoDock Tools (ADT) 1.5.6 were used to prepare the selected proteins for docking.(BIOVIA, 2016; Trott, Olson, 2010)

At first, the protein structures were prepared by removing the co-crystallized ligands. Those ligands were saved in the pdb format to be used as standards for comparing the docking results later. Then, the protein structures were imported to the AutoDock to remove the water molecules and add the hydrogen atoms and Gasteiger charges. Finally, the protein structures were saved in pdbqt format.

TABLE II - Macromolecular drug targets with their respective PDB ID and co-crystalized ligand

Target	PDB ID	Co-crystallised Ligand	Reference
Dopamine (D2)	6CM4	Risperidone	(Wang *et al.*, 2018)
Gamma-aminobutyric acid (GABAA)	6D6T	Flumazenil	(Zhu *et al.*, 2018)
N-methyl-D-aspartate (NMDA)	5U8C	PEAQX	(Romero-Hernandez, Furukawa, 2017)
Phosphodiesterase (PDE10A)	2WEY	Papaverine	(Fujishige *et al.*, 1999)

Ligand preparation

ChemSketch has been used to draw the 2D structures of the selected active constituents (ACD/ChemSketch, 2019). Whereas, Biovia DS has been used to convert the 2D structures of the compound into their respective 3D structures (BIOVIA, 2016) and the geometry was optimised using dreiding-like forcefield. Then the 3D structures of the ligands were imported into AutoDock where ADT was used to prepare the ligands for docking by adding charges, setting the rotatable bonds and allowing all the torsions to rotate for the ligands. Then, all the ligands were saved in pdbqt format.

Identification of the binding site

The amino acid residues of the prepared protein structures that involved in the interactions with the co-crystallized ligands were determined using Biovia DS (BIOVIA, 2016). The binding site of each protein structure was identified based on the determined residues. ADT was used to determine the Grid Box that covers the entire identified binding site of the protein (BIOVIA, 2016). The coordinate and size of the Grid Box were saved in the input parameter file.

Molecular docking

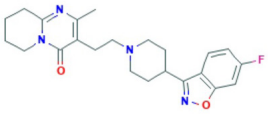
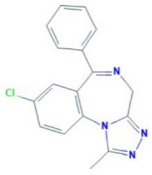
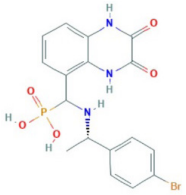
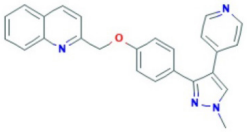
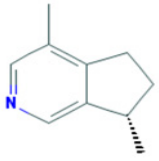
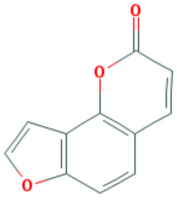
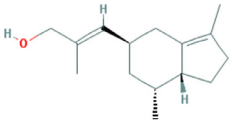
After preparing the protein structures, ligands and the input parameter file, molecular docking was performed using AutoDock Vina 1.1.2. (Trott, Olson, 2010). The prepared ligands were docked into the active sites of the prepared macromolecular drug targets. All the docking parameters have remained as default settings. The binding affinities of the standards and the ligands were recorded and compared. The binding poses of the ligands and the mode of interactions of the protein-ligand complex were studied using Biovia DS (BIOVIA, 2016).

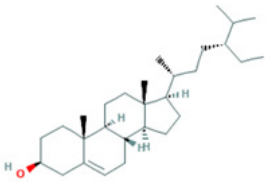
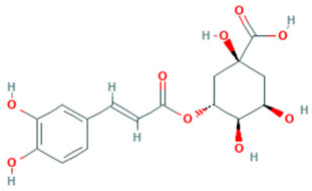
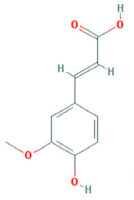
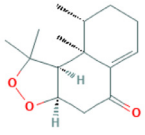
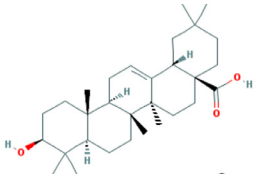
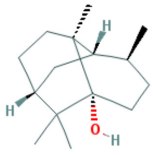
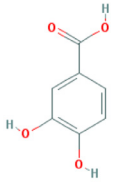
RESULTS AND DISCUSSION

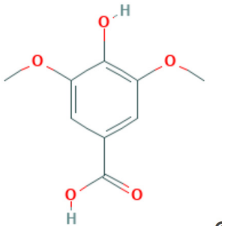
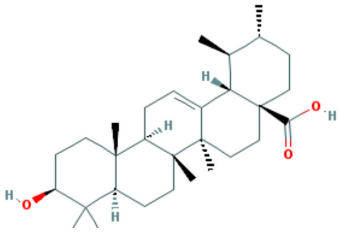
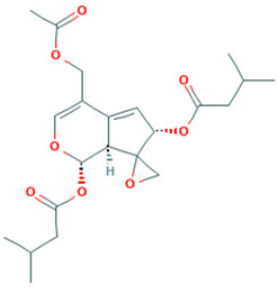
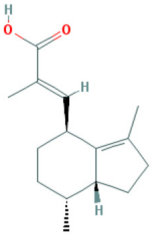
Molecular docking

The results of the docking study of the active constituents of NJ and the standard compound for each target protein are presented in Table III. As can be seen from Table III, eight ligands showed binding energies for GABAA receptor higher than the standard Alprazolam (binding energy ≤ -8.5 Kcal/mol). However, chlorogenic acid showed the highest affinity for the receptor (binding energy -9.5 Kcal/mol). While for PDE10A, oleanic acid was the only ligand exhibited binding energy for the protein (-10.6 Kcal/mol) higher than the standard MP-10 (-10.3 Kcal/mol). In contrast to GABAA and PDE10A, none of the ligands displayed binding energy for D2 receptor or NMDA higher than the standards risperidone and PEAQX. However, β-sitosterol and chlorogenic acid displayed the highest binding affinity towards D2 and NMDA, respectively (binding energy of β-sitosterol -10.1 Kcal/mol for D2 and chlorogenic acid -8.8 Kcal/mol for NMDA). Additionally, four ligands showed very low affinities toward the four receptors (binding energy > -7.00 Kcal/mol). Those ligands are octacosanol, patchouli alcohol, protocatechuic acid and syringic acid.

TABLE III - Binding energy of the standards and the active constituents of NJ towards macromolecular drug targets

Ligand	Class	Binding energy (Kcal/mol)				Structure
		D2	GABAA	NMDA	PDE10A	
Risperidone		-12.0				
Alprazolam			-8.5			
PEAQX				-10.6		
Mardepodect (MP-10)					-10.3	
Actinidine	Methylpyridines	-7.3	-7.2	-6.3	-6.0	
Angelicin	Furanocoumarins	-7.7	-8.8	-7.4	-7.5	
Aristolen-9β-ol	Sesquiterpene	-8.1	-8.6	-7.3	-7.6	

β-sitosterol	Phytosterols	-10.1	-8.6	-6.8	-8.8	
Chlorogenic acid	Ester	-8.5	-9.5	-8.8	-8.2	
Ferulic acid	Phenolic acid	-6.8	-7.2	-6.7	-6.4	
Nardosinone	Sesquiterpene	-7.9	-8.9	-7.1	-8.1	
Octacosanol	Fatty alcohol	-6.5	-6.4	-5.6	-5.3	
Oleanic acid	Pentacyclic triterpenoid	-9.0	-7.7	-7.1	-10.6	
Patchouli alcohol	Sesquiterpene alcohol	-5.8	-6.0	-5.9	-5.9	
Protocatechuic acid	Phenolic acid	-6.4	-6.8	-6.1	-5.8	

Syringic acid	Trihydroxybenzoic acid	-5.9	-6.2	-6.3	-5.9	
Ursolic acid	Pentacyclic triterpenoid	-9.8	-8.7	-2.9	-9.1	
Valepotriate	Monoterpenoid (iridoid alkaloids)	-8.3	-8.5	-7.8	-7.7	
Valerenic acid	Bicyclic sesquiterpenoid	-8.1	-8.7	-6.9	-7.7	

Dopamine (D2) receptor

Risperidone is an atypical antipsychotic that commonly uses for the treatment of schizophrenia, bipolar disorder, and irritability associated with autism. This compound has been used as the standard reference for the D2 receptor, due to the high affinity of the compound to this receptor. The binding energy of risperidone to D2 receptor was -12 Kcal/mol. The low binding energy and the high affinity of the ligand towards the D2 receptor are attributed to the halogen bond (non-covalent interaction) and the aromatic Pi-Pi T-shaped interactions (interaction between aromatic groups). The halogen bond was formed between the fluorine atom of the ligand and the amino acid residue CYS118 while the aromatic interactions were formed between the pyrimidine ring of the ligand and the TRP100 and the phenyl ring of the ligand and TRP386 and PHE390 (Figure 1).

Amongst all the ligands, β-sitosterol showed the highest binding affinity towards the D2 receptor (-10.1 kcal/mole). As shown in Figure 1, several hydrophobic interactions can be seen. Both risperidone and β-sitosterol interacted with amino acid residues VAL115 and PHE389. These three amino acids are essential for the binding of D2 antagonists as reported by a previous study (Kalani *et al.*, 2004). Further, β-sitosterol

interacted with additional residues in the hydrophobic area, these residues are VAL111, PHE189, HIS393 and TYR408. These hydrophobic interactions stabilize the ligand in the receptor's binding site. However, no hydrogen bond was involved in the interaction between β-sitosterol and D2 receptor, explaining the lower binding affinity of β-sitosterol as compared to risperidone.

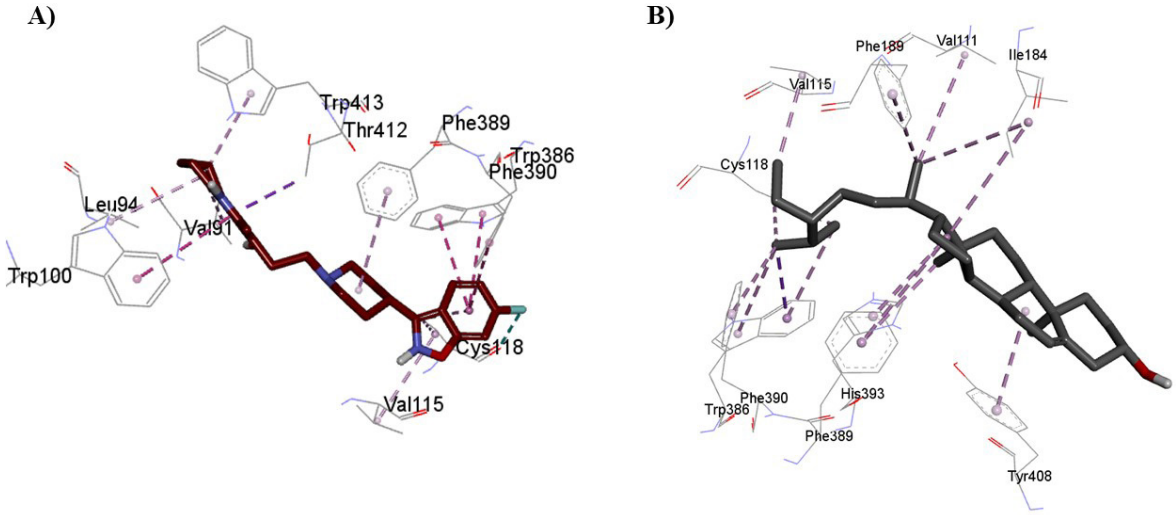


FIGURE 1 - The binding interactions between the ligands and D2 receprtor. A) Risperidone B) β-sitosterol. Halogen interaction is presented by cyan, Pi-alkyl by pink, Pi-sigma by violet and Pi-Pi stacking interactions by magenta dotted lines.

For better binding interaction, carboxylic functionality can be added to β-sitosterol. This structural modification will improve the hydrophilicity of the ligand and provides better hydrogen bonding interaction as well (Chung, Choi, 2007).

Apart from β-sitosterol, oleanic acid and ursolic acid also displayed high binding affinity towards D2 receptor, with the binding energies of -9.0 kcal/mole and -9.8 kcal/mole, respectively. Oleanic acid and ursolic acid are classified in triterpene subgroup. Some structural similarities can be found in the structures of β-sitosterol, oleanic acid and ursolic acid as triterpenes are the precursors of steroids. Both steroid backbone and pentacyclic triterpene structures formed van der Waals forces and hydrophobic interactions with the amino acid residues of the D2 receptor. This explains the binding preference of the D2 receptor towards the steroid backbone and pentacyclic triterpene structures.

Gamma-aminobutyric acid (GABAA) receptor

Alprazolam is a short-acting benzodiazepine that commonly uses in short term management of anxiety disorders. In addition, it is used as an adjunct therapy during emergency treatment of schizophrenia (Barbee *et al.*, 1992). This compound has been used as a standard reference for the GABAA receptor. The binding energy of alprazolam to GABAA was -8.5 kcal/mole. The good affinity of the ligand to the GABAA receptor was attributed to the hydrophobic and aromatic interactions. Where TYR210 was involved in these interactions. Other amino acids were also involved in protein-ligand interactions. These amino acids are PHE100, TYR58, TYR160 and HIS102 (Figure 2).

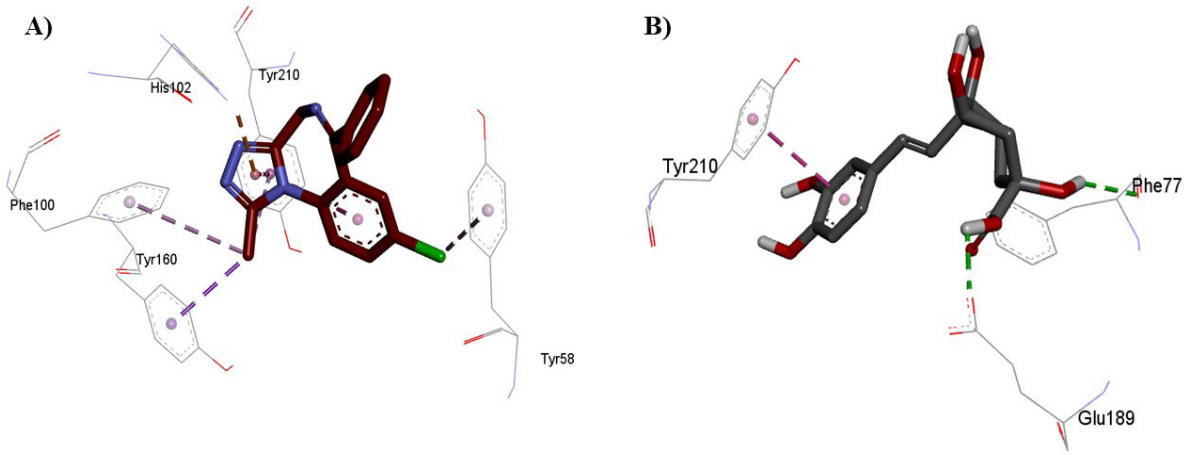


FIGURE 2 - The binding interactions between the ligands and GABAA. A) Alprazolam B) Chlorogenic acid. Hydrogen bonds are presented by green, Pi-alkyl by pink, Pi-cation by orange, Pi-sigma by violet and Pi-Pi stacking interactions by magenta dotted lines.

Chlorogenic acid exhibited the highest binding affinity towards the GABAA receptor (-9.5 kcal/mole). As can be seen in Figure 2, the ligand formed two hydrogen bonds with the binding site's residues. These hydrogen bonds formed between the carboxyl and the hydroxyl groups of the ligand and the residues GLU189 and PHE77, respectively. The two hydrogen bonds stabilize the ligand in the active site of GABAA and resulted in a superior binding affinity of chlorogenic acid as compared to the standard ligand, alprazolam.

On the other hand, Pi-Pi stacking interaction was formed between the catechol group of chlorogenic acid and the aromatic ring of residue TYR210. This interaction is similar to the one observed with alprazolam and GABAA and it is important to determine the preferred orientation of the ligand in the binding site of the GABAA receptor.

To improve the binding affinity of chlorogenic acid towards the GABAA receptor, tetrazole was suggested to replace the carboxyl group (Figure 3). This modification is expected to improve the lipophilicity of the ligand and resulted in a better CNS penetration. Together with chlorogenic acid, both angelicin and nardosinone showed good binding affinities towards the GABAA receptor with binding energies -8.8 Kcal/mol and -8.9 Kcal/mol, respectively.

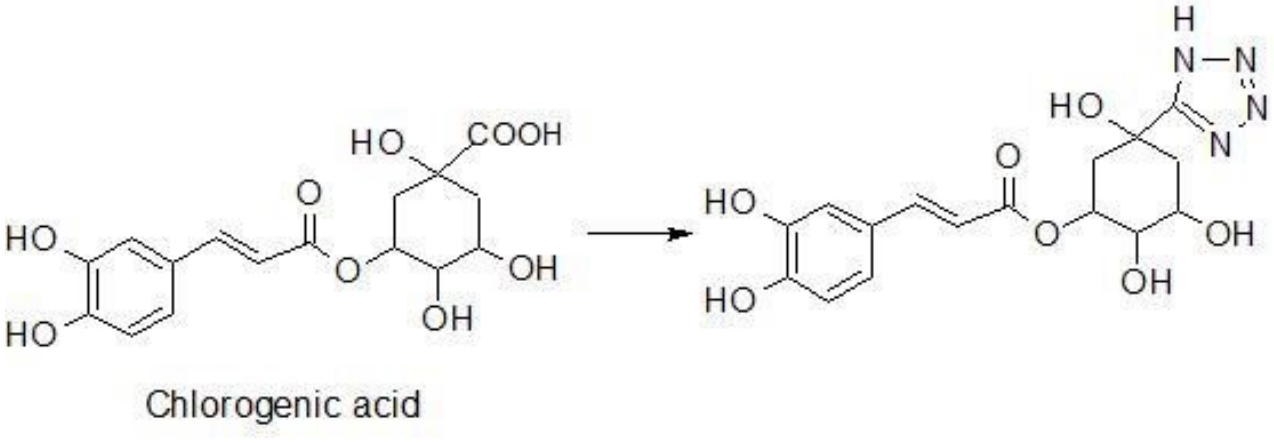


FIGURE 3 - Replacement of carboxyl group with tetrazole.

N-methyl-D-aspartate (NMDA) receptor

The selected 3D structure of the NMDA receptor (PDB ID: 5U8C) was co-crystallized with glycine and PEAQX, a glutamate site antagonist. This original co-crystallized ligand was directly used as the standard reference for NMDA receptor as there was no suitable NMDA agonist available. Glycine was not removed upon docking as it acted as a co-agonist to facilitate the effect of glutamate site agonist.

PEAQX has high affinity to NMDA receptor with binding energy -10.6 Kcal/mol. The high affinity is attributed to the six hydrogen bonds and the hydrophobic interactions formed between the ligand and the binding site residues. The hydrogen bonds were formed between the three oxygen atoms of the phosphate group and TYR214, THR174 and SER173, the hydroxyl group and SER173, the oxygen group and THR116 and the secondary amine and SER114. All the amino acid residues were acted as hydrogen bonds donor (Figure 4). While the hydrophobic interactions were formed between the ligand and the two amino acid residues ILE136 and HIS88.

The chlorogenic acid displayed the highest affinity not only for the GABAA receptor but also for the NMDA receptor. It showed the lowest binding energy to NMDA (-8.8 Kcal/mol) among the rest of the compounds. This ligand was involved in seven hydrogen bonds with the binding site residues. The hydrogen bonds were formed between the four hydroxyl groups of the ligand and the residues HIS88, GLU16, SER114, ALA241 and ASN118 and between the oxygen atom of the carboxyl group and residue ASN177 (Figure 4). Both PEAQX and chlorogenic acid showed a hydrogen bond interaction with SER114 and Pi-hydrophobic interaction with ASP215. These interactions contributed to the high affinities of the ligands to the target receptor.

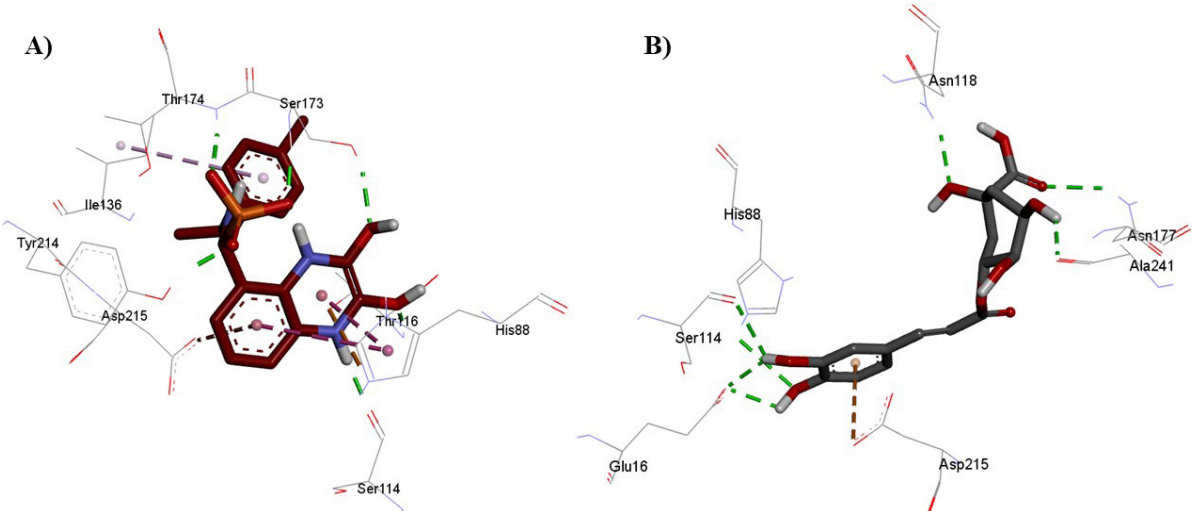


FIGURE 4 - The binding interactions between the ligands and NMDA receptor. A) PEAQX B) Chlorogenic acid. Hydrogen bonds are presented by green, Pi-alkyl by pink, Pi-cation/anion by orange, and Pi-Pi stacking interactions by magenta dotted lines.

For a stronger binding interaction, the replacement of the hydroxyl group in chlorogenic acid by urea bioisosteres, NHCONH2 or NHCOCH3 is recommended where Patani *et al*. suggested that these electron-donating substituents are more advantageous in hydrogen bond formation as compared to the hydroxyl group (Figure 5) (Patani, LaVoie, 1996).

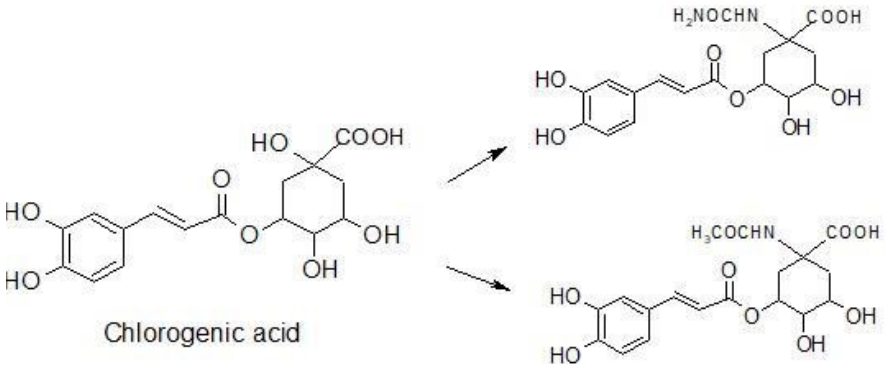


FIGURE 5 - Replacement of the hydroxyl group with urea bioisosteres.

Phosphodiesterase (PDE10A) receptor

Mardepodect or MP-10 is a selective PDE10A inhibitor that has been developed by Pfizer for the treatment of schizophrenia (Verhoest *et al.*, 2009). MP-10 has high affinity and selectivity for PDE10A over the other PDE families. Thus, it has been selected as a standard reference for PDE10A receptor.

In the present docking study, MP-10 has shown low binding energy to PDE10A (-10.3 kcal/mole). The ligand displayed several types of interactions with different amino acid residues. First, the HIS525 was involved in two hydrogen bonds interactions where it acted as a hydrogen bond donor. The first hydrogen bond formed with the oxygen atom of MP-10 while the second hydrogen bond formed with the nitrogen atom of the ligand. Second, the catechol group of MP-10 formed Pi-Pi stacked interaction with the aromatic ring of PHE729. Further, the ligand involved in hydrophobic interactions with the amino acid residues ILE692, VAL678 and LEU635 (Figure 6).

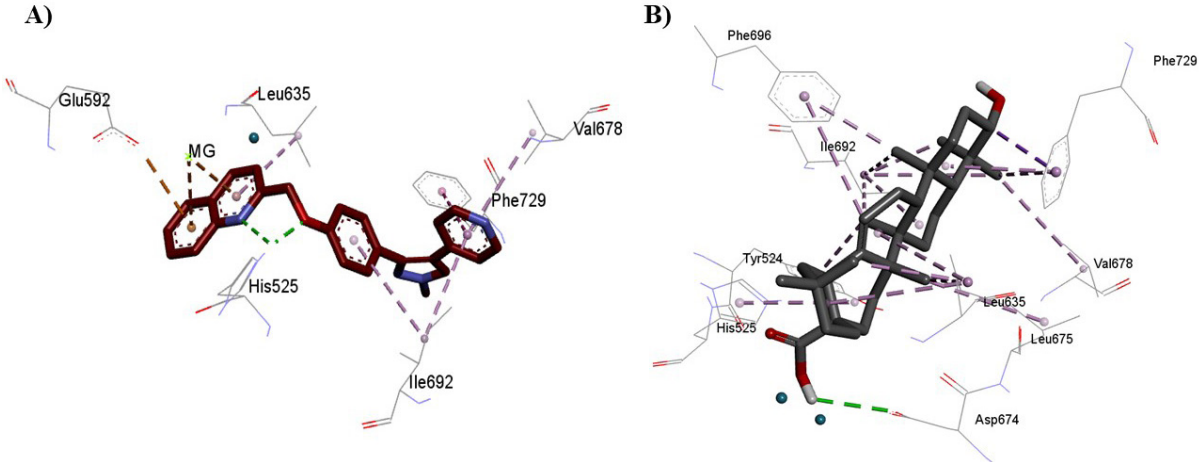


FIGURE 6 - The binding interactions between the ligands and PDE10A receptor. A) MP-10 B) Oleanic acid. Hydrogen bonds are presented by green, Pi-alkyl by pink, Pi-cation/anion by orange, Pi-sigma by violet and Pi-Pi stacking interactions by magenta dotted lines.

Oleanic acid was the only ligand displayed binding energy to PDE10A (-10.6 Kcal/mol) higher than that of the standard MP-10. As can be seen in Figure 6, there were numerous binding interactions between oleanic acid

and amino acid residues. These interactions involved a hydrogen bond between the hydroxyl group of the ligand and the amino acid residue ASP674. Hydrophobic interactions with the residues LEU675, HIS525, TYR524, ILE692, VAL678, LEU635 and PHE696.

ILE692, PHE729 and PHE696 form the hydrophobic clamp (P-clamp) which is important for stabilizing the ligand in the binding site of PDE10A. Oleanic acid interacted with the three residues while MP-10 interacted with two residues only, ILE692 and PHE729. Thus, oleanic acid showed a higher affinity for PDE10A as it occupied the P-clamp and interacted with the main amino acid residues.

Hydroxamic acid is suggested to replace the carboxyl group in oleanic acid for better binding affinity towards the PDE10A enzyme (Figure 7). Similar to the carboxyl group, hydroxamic acid shows a good hydrogen bond environment (Thakur, Patre, Pande, 2012). Besides being employed successfully as a carboxylic acid bioisostere, this functional group has been used in drug design for its metal-chelating properties (Ballatore, Huryn, Smith III, 2013).

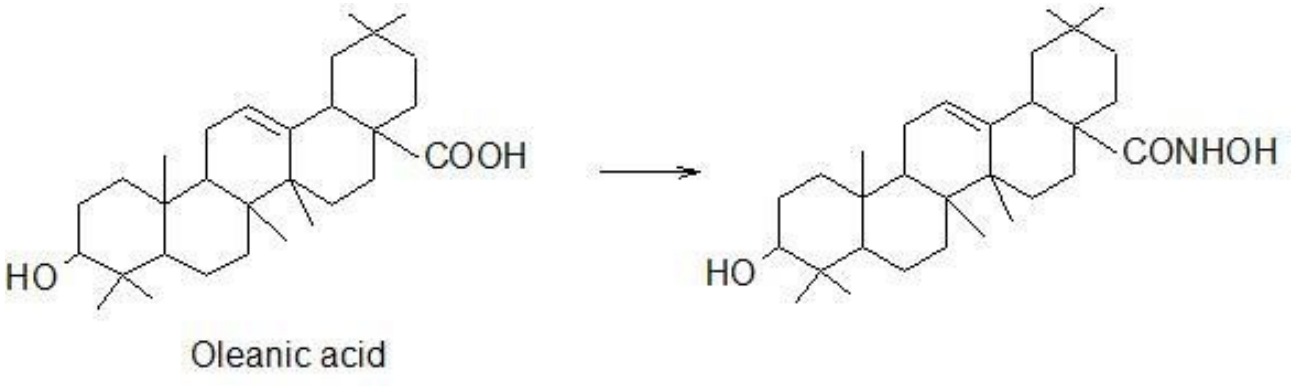


FIGURE7 - Replacement of carboxyl group with hydroxamic acid.

β-sitosterol and ursolic acid showed high binding affinities for PDE10A as well, with binding energies of -8.8 Kcal/mole and -9.1 Kcal/mole, respectively. These three ligands were the same ligands that displayed the highest affinities for the D2 receptor. This suggests that both the steroid backbone and pentacyclic triterpene structure have an advantageous binding affinity towards both the D2 and PDE10A receptors.

CONCLUSION

The molecular docking study reported here assists in illustration the active constituents of the *Nardostachys jatamansi* that have high affinities to the main macromolecular drug target involved in the pathophysiology of schizophrenia. Almost all the active constituents showed good binding affinities to the four macromolecular drug targets, D2, GABAA, NMDA and PDE10A, except four compounds which showed binding energy > -7 Kcal/mol. β-sitosterol, chlorogenic acid, oleanic acid and ursolic acid demonstrated significantly higher affinities to the four targets in comparison to the rest of the ligands. The four ligands were involved in several interactions with the binding site residues of each receptor. Each macromolecular drug target has its ligand structural preferences. For example, ligands with steroid backbone and pentacyclic triterpene structure showed superior binding affinities towards D2 receptor and PDE10A enzyme. In contrast, ligands with carbonyl group formed stronger binding interactions with NMDA receptor.

Molecular dynamics simulations can be conducted to study the stability of the four ligands within the binding sites of the target macromolecular drug targets. The information derived from these studies will assist in designing of more powerful compounds. These compounds can be further evaluated *in vitro* and *in vivo.*

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