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Structure-based virtual screening of phytochemical for dopamine D_2 receptor ligands as future antipsychotics: An ayur-informatics approach

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Abstract

Background: Schizophrenia is a severe mental disorder, which affects more than 21 million people globally. This disease is characterized by distortions in thinking, emotions, perception, and behavior. There is no cure for schizophrenia till date; dysregulation of the dopaminergic system is etiologic for schizophrenia. The treatment involves the use of antipsychotic drugs that act by blocking the dopamine receptor thus help in elevating the symptoms.
Methods: In this study molecular docking method was used to explore the binding mechanism of phytochemicals present in Ayurveda medicinal herbs that are being traditionally used for the treatment of mental condition like Schizophrenia. Natural products have historically & continuously been explored for novel promising leads in pharmaceutical development.
Results: Screening of natural compounds like Withaferin A, Withanolide, Rutin and Reserpine against dopamine receptor (D2) showed very promising results. These compounds have a higher docking score in comparison with already marketed antipsychotic drug.
Conclusion: Phytochemicals screened in this study can be investigated further for their role as antipsychotics. This study highlights the importance of traditional Indian medicine system "Ayurveda" in finding the possible hits that can be used for the treatment of Schizophrenia.
Keywords: Dopamine receptor D2, Schizophrenia, Ayurveda, AutoDock Vina, Virtual screening, Molecular docking, Medicinal plants, Ligand receptor interaction, Ayur-informatics.

1. Introduction

Schizophrenia is 'third most disabling disorder which affects 0.5–1.5% of the worldwide population, hence became a challenge for modern medicine [1]. This disease is characterized by delusions, hallucinations, disorganized behavior, and cognitive difficulties such as memory loss of the many contemporary theories of schizophrenia, the most enduring has been the dopamine hypothesis of psychosis-in-schizophrenia [2], which states that the dysregulation of the dopaminergic system is etiologic for schizophrenia. Excess transmission at dopamine receptors lead to striatal dopamine hyper-function and blockade of these receptors can be used as drug target to treat the dopamine dysregulation [3]. Many researches on antipsychotic dopamine D2 receptor led to a validation in confirmation that it is the primary site of action and act as the targets for developing drugs. Antipsychotic drugs are the mainly used for almost six decades for the treatment of Schizophrenia. But, unfortunately these drugs have severe side effects.

Therefore, indeed discovered safe & effective antipsychotics therapeutic agents. The role of Ayurveda in the treatment of mental illness, however, dates to the Vedic period (c. 1000 BC) and it is still being used as the sole treatment or in conjunction with antipsychotic medication in developing as well as developed countries. The ayurvedic pharmacopoeia of India provides insight on specific properties of plants and their use in the treatment of various diseases. A very few studies have been reported globally, that employed the use of *In-silico* approach to find new lead compound against different target that are involved in the pathophysiology of Schizophrenia.

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In [4] tried to identify novel competitive antagonists of the dopamine D2 receptor & [5] used the bioinformatics approach for schizophrenia targeting RGS4 gene. In [6] explored the arylpiperazine derivatives as promising 5-HT2A antagonists. QM/MM Refinement study of Haloperidol Binding to the Human Dopamine D3 Receptor was performed by [7]. Only two studies reported in India yet, used the bioinformatics approach for schizophrenia targeting RGS4 gene. Modulation of the N-methyl-D-aspartate receptor by amino acid oxidase activator (DAOA) was studied by [8].

Since the etiology of schizophrenia is complex involving multiple proteins there is a need for developing more potent and safer antipsychotics. In present study, we explore the application of phytochemicals from medicinal plants like Mandukparni (*Centella asiatica*), Chandan, Jatamansi (*Nardostachys jatamansi*), Ashwagandha (*Withania somnifera*), Sankhpushpi (*Convolvulus pluricaulis*), Brahmi (*Bacopa monnieri*), Sarpagandha (*Rauwolfia serpentina*) [9-11] in treatment of schizophrenia-related disorders.

These medicinal plants have been already used traditionally for the treatment of Manasa Vikara (impairment of mental functions). Furthermore, by intensive literature study using search engines like Pub Med, Medline and Cochrane, we identified the major phytochemical responsible for their therapeutic properties and investigated their role as antipsychotic by screening against D2 receptor. Furthermore, in this paper we identify active phytochemical constituents giving pharmacological activity to traditional medicinal herb.

2. Objectives of this study

Identify active phytochemical constituent providing pharmacological activity to traditional medicinal herb through online search engine & screening them against D2 receptor for schizophrenia treatment.

3. Methodology

Structure-based virtual screening method was employed in this study. Structure of our target Dopamine (D2) receptor was downloaded from Protein Data Bank (PDB ID-6CM4). Bound ligand, water molecules were removed and hydrogen atoms were added to the receptor molecule and finally converted into PDBQT format for docking. 3D structures of ligands i.e. FDA approved Antipsychotic drugs (Table 1) & natural phytochemicals (Table 2) were accessed from PubChem, energy minimization was performed using Open Babel and converted to PDBQT format.

Table-1, Docking score of reference compounds (Antipsychotic Drugs) with D2 dopamine receptor

S.No.		DRUG	SCORE
1.		Pimozide	-7.8
2.		Haloperidol	-7.3
3.		Loxapine	-7.2
4.		Thiothexine	-7.1
5.		Fluphenazine	-7
6.		Trifluoperazine	-7
7.		Thioridazine	-6.7
8.		Perphenazine	-6.4
9.		Molindone	-6.2
10.		Prochlorperazine	-6.2
11.	1st generation Antipsychotic	Chlorpromazine	-5.7
12.		Olanzapine	-8.4
13.		Quetiapine	-8.3
14.		Lurasidone	-8
15.		Iloperidone	-7.6
16.		Aripiprazole	-7.3
17.		Brexpiprazole	-7.2
18.		Cariprazine	-7.2
19.		Clozapine	-7.2
20.		Paliperidone	-6.9
21.	2^{nd} generation Antipsychotic	Asenapine	-6.8
22.		Risperidone	-6.3

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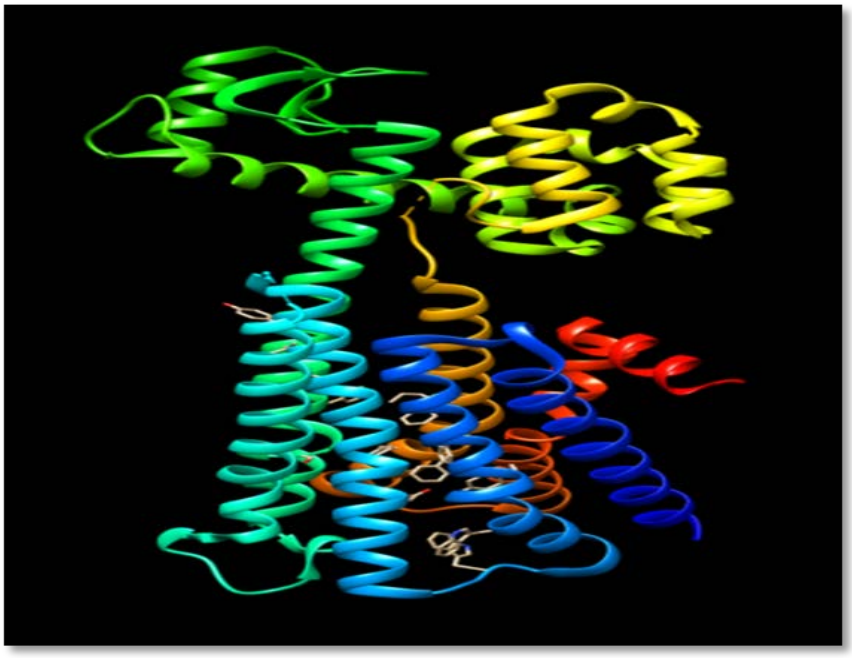
The virtual screening was performed using PyRx software, which includes Auto dock vina [12]. The Lamarckian genetic is used as a scoring algorithm. Grid Parameter of center-: X-17.6817, Y-1.4380, z-14.9681 & dimensions (Å)-: X-73.8169, Y-56.0509, Z-78.8813 was used.

In [13] and Discovery studio software was used for analysis of docking results. For each docked molecule Auto dock Vina showed different binding positions, we selected the binding mode with the best score. Docking score of already approved antipsychotics drugs both typical & atypical were used as a reference for our docking study.

Table 2, Docking score of natural phytochemical (Ayurvedic) with D2 receptor

S. No.	Drug	Score
1	Withaferin A	-8.7
2	Withanolide	-8.7
3	Rutin	-8.1
4	Reserpine	-8
5	Stigmasterol	-8
6	beta-Sitosterol	-7.8
7	Brahmic acid	-7.7
8	Asiatic Acid	-7.6
9	Quercitrin	-7.5
10	Stepholidine	-7.2
11	Kaempferol	-7.1
12	Nardosinone	-6.9
13	Jatamansin	-6.8
14	4-O-CAFFEOYLQUINIC-ACID	-6.7
15	Chlorogenic Acid	-6.7
16	beta-Eudesmol	-6.6
17	Angelicin	-6.4
18	Convoline	-6.4
19	Jatamansone	-6.3
20	Scopoletin	-5.8
21	Anahygrine	-5.3
22	Anaferine	-5.1
23	Cuscohygrine	-5
24	2,3-Xylidine SAPONINS	-4.8
25	Isopelletierin	-4.8

Figure 1. Structure of D2 receptor (PDB ID-6CM4)



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4. Results

Results are summarized in Tables (1,2) and Figures (1-3) provided in the end of this article. Comparison of binding affinities and interactions of standard antipsychotic drugs and Phytochemicals for D2 receptor (PDB ID-6CM4) provided.

Figure 2. A- D2 receptor interaction with Withanolide (-8.7), B- Amino acid residues involved in interaction of Withanolide & D2 receptor, C- Reserpine (-8.0) interaction with D2 receptor, D- 2 D interaction diagram of Reserpine with D2

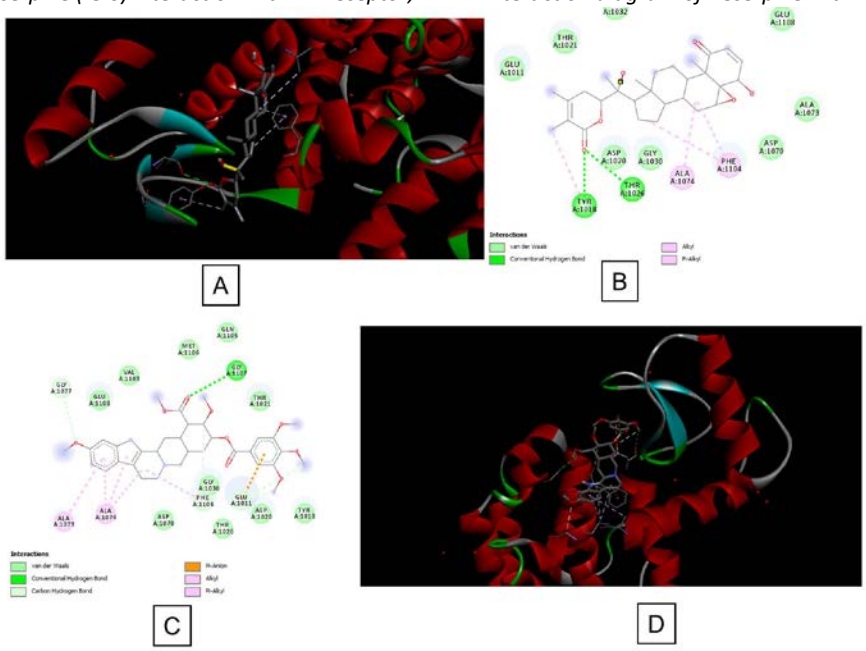
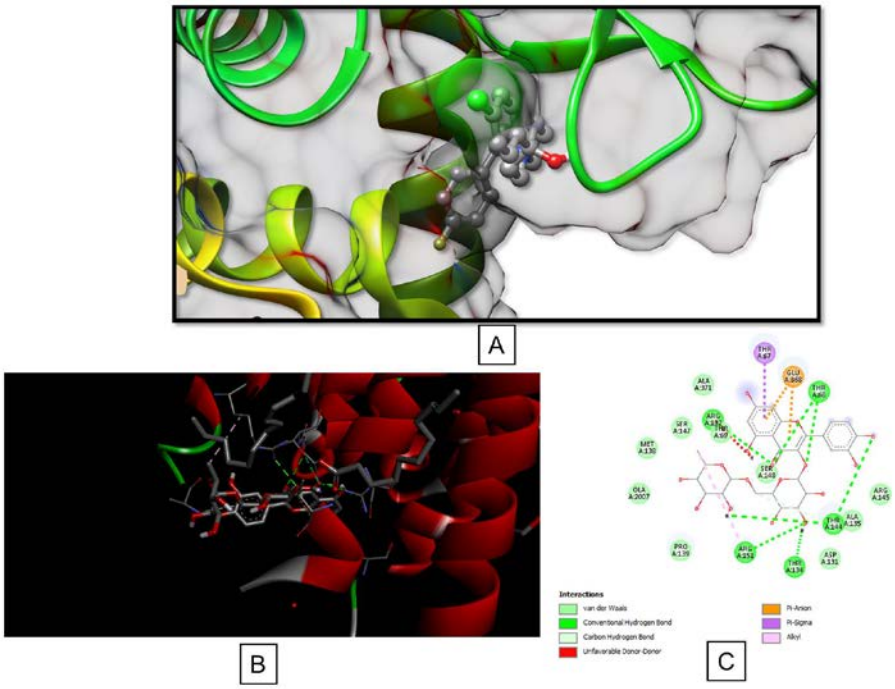


Figure 3. A- D2 receptor interaction with Haloperidol (-7.3), B- Visualization of D2 receptor interaction with Rutin (-8.1), C- Amino acid residues involved in interaction (2-D diagram)



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5. Discussion

Schizophrenia is one of the most burning problems of the globe. Multiple evidence including recent imaging studies have suggested that imbalance of the dopaminergic system i.e the hyper stimulation of striatal dopamine D2 receptors is responsible for psychosis. Antipsychotics are mainly used in the pharmacologic treatment of schizophrenia. Many Ayurvedic herbs like Sarpagandha, Jatamansi, Brahmi, Mandukparni (Thankuni) and Ashwagandha are used over decades to treat several mental conditions with their special mention in *Charaka Samhita* which is a text book on the traditional system of Indian medicine. Docking studies are frequently used to predict the binding affinity of the small drug molecule to their protein, which is the basis of rational drug design process.

In this study, preliminary *In-silico* screening of natural phytochemical that are believed to have some potential to inhibit D2 receptor was performed. Virtual screening of phytochemicals like Withanolide, Withaferin-A, Reserpine, Stepholidine, Stigmasterol, Rutinand, Quercitrin against D2 receptor shows very promising results shown in Table 2. We try to compare the docking score of already approved antipsychotics (Table 1) in the market with natural phytochemicals (Table 2). Comparative docking shows that some of these compounds like Withaferin-A(-8.7), Withanolide(-8.7), Reserpine(-8.0), Rutin(-8.1) from Ayurveda medicinal plants have the high docking score than that of already approved psychotic drugs like Lurasidone(-8.0), Olanzapine(-8.4) & Quetiapine(-8.3) in the market. We also observed that Chlorpromazine which has a score of -5.7 is an approved antipsychotic and most of our investigated phytochemical have a score higher than that of Chlorpromazine. So this information supports that these phytochemicals will be very effective and can be investigated further for developing novel compounds having better antipsychotic activity.

Moreover we also try to study the interaction between the residues of D2 receptor present in the binding pocket and our investigated ligands by 2-D interaction diagram and find out that among all the compounds Rutin is interacting with maximum number of residues as evident from Fig- 3C. This information on interacting residues involved in the ligand receptor binding can help us in pharmacophore modeling, and in optimization of our lead compounds to make them more specific & potent.

Further in-vitro & in-vivo studies can be performed to check their effectiveness for developing new medication for schizophrenia. Still there is a scope of evaluating the roles of these phytochemicals with different targets like D3, D4 & 5-HT involve in the path physiology of Schizophrenia disease. Some earlier attempts on virtual screening of the Enamine compound database has been made in order to identify new active compounds and also they have identified some hundreds of compounds but no further progress in this direction has been reported and this is for the first time we tried to explore the natural compounds from Ayurveda medicinal plants for their role as antipsychotics.

6. Conclusion

Our study highlights the importance of Indian Ayurveda medication system towards developing new leads for Schizophrenia. In-silico approach & bioinformatics tools have the potential to speed up the drug discovery process, reducing the cost and also change the way in which drugs are designed. Withaferin-A (-8.7), Withanolide (-8.7), Reserpine (-8.0) and Rutin (-8.1) have the potential to be investigated further; the treatment based on the integration of Ayurveda and allopathic can be used to increase the therapeutic effects with lesser side effects

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