Ayur-Informatics-Establishing Ligands for Schizophrenic Receptors from Ayurvedic Medicinal Herbs

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Abstract. Schizophrenia is a chronic psychiatric disorder with a heterogeneous genetic and neurobiological background, it is one of the mental disorder which is common all over the world. Genes associated with Schizophrenia are DRD2, ERBB4, GRIA1, GRIN2A, GRM3. Among its related pathways/superpathways are Dopaminergic synapse and Neuroactive ligand-receptor interaction used in this work. Plant phytocomponents used in this work: *Withania sominifera, Melisa officinalis, Pipermethysticum, Veleriana and Hypericum perforatum.* Using swiss model server homology modelling was done to the schizophrenic receptors using molinspiration server, phytocompounds were shortlisted based on Lipinski's rule of five. Further docking was done with the phytocompounds as selected by molinspiration server with the schizophrenic receptors.

Keywords: Schizophrenia · Ayurveda · genes · docking · ligand-receptorinteraction · phytocomponents · homology modelling

1 Introduction

Schizophrenia is a chronic psychiatric disorder with a heterogeneous genetic and neurobiological background that influences early brain development, and is expressed as a combination of psychotic symptoms — such as hallucinations, delusions and disorganization — and motivational and cognitive dysfunctions wherein a person has difficulty to think properly [1, 2]. The person has difficulty to distinguish between reality and imagination [1, 2]. It is often shown in adolescence or early childhood. They have difficulty in expressing normal emotions [1, 2]. As per Ayurveda, Schizophrenia is known as Unmaad [1, 2]. It is similar to atatwabhinivesh in Ayurveda [3]. According to Ayurveda there are three physical energies (vata, pitta and kapha) are responsible for healthy life [3, 4]. Imbalance of any psychic energies (satva, raja, tama) supported by imbalance of physical energies (vata, pitta, kapha) are believed to cause various mental disorders like schizophrenia [3, 4]. According to Maharshi Charaka, the person who has vitiated doshas evade the person's brain whose mind is under rajasik and tamasik influences and

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Table 1. Genes with their NCBI Accession number

Sl. No	Gene Receptors	NCBI Accession Number	Homologous Template
1.	DRD2	P14416.2	7JVRA
2	ERBB4	AAI43750	3U7UA
3	GRIA1	P42261	71DDA
4	GRIN2A	AAI17132.1	6MMPD
5	GRM3	AAH22496.2	2E4UA

block channels of mind and nerve impulses [3, 4]. It affects the functioning of brain and intelligence. In that case person fails to differentia between real and imaginary world [2–4]. Schizophrenia with or without an affective disorder, is related to schizo affective disorder and paranoid schizophrenia, and has symptoms including photophobia, restlessness and personality changes [2–4].

2 Materials and Methods

Drug design is the whole process of taking a newly discovered compound or drug molecule. Structure based drug designing technique is used here to build, display, simulate and analyze the molecular structure. Here we have used SWISS-MODEL [5] tool for modelling the proteins (gene receptors) responsible for schizophrenia DRD2, ERBB4, GRIA1, GRIN2A, GRM3. Selected models from homology modelling output are docked with selected phytocompound from medicinal herbs. Selection of phytocompounds was done using Lipinski rule for drug which is based on the ADME properties. Molecular docking was done using Patchdock [6, 7] tool and best interacting phytocompounds with the gene receptors can be selected as ligands.

3 Results and Discussion

Since, schizophrenia is chronic psychiatric disorder with a heterogeneous genetic and neurobiological background, we further go ahead towards designing novel drug for the disease. Corresponding gene receptors are taken from NCBI for our work (Table 1).

Abbreviations of genes:

1. DRD2: Dopamine receptor D2
2. ERBB4: Receptor tyrosine kinase erB4
3. GRIA1: AMPA receptor subunit 1(GluA1; GluR1)
4. GRIN2A: NMDA receptor subunit 2A (GluN2A-NR2A)
5. GRM3: metabotropic glutamate receptor(mGlu3)

Homology Modeling

Homology modeling of the above receptors are done using SWISS-MODEL server. Template used for modeling is given in Table 1. Ayurvedic Medicinal plants *Withania*

Table 2. ADME studies with *Withania Somnifera*

SL. NO	Compounds	MiLogp	TSPA	Natoms	mw	nON	nOHNH	N-Violations	nROTB	VOLUME
1	o-bromotropine	2.06	49.77	22	368.27	4	1	0	5	296.90
2	azetidin	-0.37	55.12	10	142.20	3	3	0	1	144.31
3	d-allose	-2.64	110.37	12	180.16	6	5	0	1	151.81
4	2-methoxy-4-vinyl phenol	2.13	29.46	11	150.18	2	1	0	2	145.34

Table 3. ADME studies with *Melisa officinalis*

SL. NO	Compounds	MiLogp	TSPA	Natoms	mw	nON	nOHNH	NViolations	nROTB	VOLUME
1	linalool	3.21	20.23	11	154.25	1	1	0	4	175.59
2	neral	3.65	17.07	11	152.24	1	0	0	4	169.74
3	sulactone	2.31	17.07	9	126.20	1	0	0	3	142.32
4	geranial	3.65	17.07	11	152.24	1	0	0	4	169.74
5	citronelal	3.60	17.07	11	154.25	1	0	0	5	175.95
6	sabinene	3.02	26.30	14	196.29	2	0	0	3	202.23
7	beta-pine	3.24	17.07	14	192.30	1	0	0	2	204.74

Table 4. ADME studies with *Piper methysticum*

SL. NO	Compounds	MiLogp	TSPA	Natoms	mw	nON	nOHNH	N-Violations	nROTB	VOLUME
1	5-hydroxy-4,7-dimethoxy flavanone	3.19	65.00	22	300.31	5	1	0	3	265.32
2	mattecinol	3.40	66.76	21	284.31	4	2	0	1	255.37
3	tetrahydroyangonin	2.19	44.77	19	262.31	4	0	0	5	246.91
4	yangonin	3.37	48.68	19	258.27	4	0	0	4	234.51

somnifera [8], *Melisa officinalis* [9], *Piper methysticum* [11], *Veleriana officinalis* [12] and *Hypericum perforatum* [13] are traditionally used to treat many diseases, such as wide variety of illneses asthma, dibeates, arthritic diseases and cancer. The potency of their phytocompounds in treating schizophrenia disease is studied here.

As per Lipinski's rule of five [ADME (Adsorption, distribution and metabolism extraction)] we check the drug likeliness of the above phytocompounds (Table 3–8).

Molecular Docking

Further docking is performed with the receptor in Table 1 with the above phytocompounds (Table 2, 3, 4, 5, 6, 7 and 8). Receptor (protein), compound, docking score, interacting amino acid and number of interaction are noted in Table 9, 10, 11, 12, 13 and 14.

Table 5. ADME studies with *Veleriana officinalis*

SL. NO	Compounds	MiLogp	TSPA	Natoms	mw	nON	nOHNH	N-Violations	nROTB	VOLUME
1	Veleric acid	3.92	37.30	17	234.34	2	1	0	2	240.16
2	Isovaleric acid	1.21	37.30	7	102.13	2	1	0	2	106.39
3	Bornyl acetate	3.05	26.30	14	196.29	2	0	0	2	202.23
4	valerianol	3.99	26.23	16	222.37	1	1	0	1	234.30
5	Myrtenyl acetate	3.0	26.30	14	194.27	2	0	0	3	196.58

Table 6. ADME studies with *Hypericum perforatum*

SL. NO	Compounds	MiLogp	TSPA	Natoms	mw	nON	nOHNH	N-Violations	nROTB	VOLUME
1	Caryophyllene oxide	4.14	12.53	16	220.36	1	0	0	0	234.01
2	Spathulenol	3.91	20.23	16	220.36	1	1	0	0	233.07
3	Hydrocarbon	3.44	49.69	19	274.47	3	2	0	12	304.92

Table 7. Withania sominifera

SL. NO	RECEPTOR (PROTEIN)	COMPOUND	DOCKING SCORE (-Kcal/mol)	INTERACTING AMINO ACID	NO OF INTERA-CTION
1.	**7JVRA**	o-bromotropine	-4660	ILE-184, SER-197, LTS369	3
2.		Azetidine	-3204	GIU-280, GLN-277	2
3.		D-Allose	-2832	ARG-230, MET-283, ASN-224, ALA-276	4
4.		2-methoxy-4-vinylphenol.	-3218	ARG-230, ASN-224	2
5.	**3U7UA**	o-bromotropine	-4108	SER-527	1
6.		Azetidine	-2700	CYS-520, GLN-448, LEU-521	3
7.		D-Allose	-2530	ASN-34, GLN-45	2
8.		2-methoxy-4-vinylphenol.	-2740	CYS-520, ASN-363	2
9.	**71DDA**	o-bromotropine	-4336	ASN-805, GLU-641	2
10.		Azetidine	-2704	PHE-113, SER-156	2
11.		D-Allose	-2394	THR-798, LYS-797, GLU-641	3
12.		2-methoxy-4-vinylphenol.	-2882	SER-156	1

(*continued*)

Table 7. (*continued*)

SL. NO	RECEPTOR (PROTEIN)	COMPOUND	DOCKING SCORE (-Kcal/mol)	INTERACTING AMINO ACID	NO OF INTERA-CTION
13.	**6MMPD**	O-bromotropine	-3148	GLU-315, PHE-121	2
14.		Azetidine	-4652	ILE-313	1
15.		D-Allose	-2888	HIS-332, GLU-315, ILE-313	3
16		2-methoxy-4-vinylphenol.	-3200	PHE-121	1
17.	**2E4UA**	o-bromotropine	-4882	THR-118, ARG-114, TYR-125	3
18.		Azetidine	-3072	VAL-120, ASP-121, ARG-114	3
19.		D-Allose	-2914	SER-610, GLY-611, GLU-767	3
20		2-methoxy-4-vinylphenol	-3296	GLY-611	1

Table 8. Melisa officinalis

SL. NO	RECEPTOR (PROTEIN)	COMPOUND	DOCKING SCORE (-Kcal/mol)	INTERACTING AMINO ACID	NO OF INTERA-CTION
1.	**7JVRA**	Linalool	-3582	ASN-224	1
2.		Neral	-3192	ASN-143	1
3.		Sulactone	-2970	ASN-224	1
4.		Geranial	-3870	GLU-78, GLU-280	2
5.		Citronelal	-3332	SER-228	1
6.		Sabinene	-3794	ARG-220	1
7.		Beta-pine	-3862	GLU278, GLU280	2
8.	**3U7UA**	Linalool	-3170	CYS520	1
9.		Neral	-3166	SER-310	1
10.		Sulactone	-2678	GLN-448, CYS-520, ASL-518	3
11.		Geranial	-3100	CYS523	1
12.		Citronelal	-3306	CYS308	1

(*continued*)

Table 8. (*continued*)

SL. NO	RECEPTOR (PROTEIN)	COMPOUND	DOCKING SCORE (-Kcal/mol)	INTERACTING AMINO ACID	NO OF INTERA-CTION
13.		Sabinene	-3316	LYS-451, LEU-521, CYS-520	3
14.		Beta-pine	-3130	GLU-82, ARG106	2
15.	**71DDA**	Linalool	-3046	SER-112	1
16.		Neral	-3146	SER-156	1
17.		Sulactone	-2868	PHE-113	1
18.		Geranial	-3130	ASN-95	1
19.		Citronelal	-3188	TYR-288	1
20.		Sabinene	-3440	SER-112	1
21.		Beta-pine	-3274	ARG-126	1
22.	**6MMPD**	Linalool	-3418	SER-132, TYR-281	2
23.		Neral	-3738	PHE-121	1
24.		Sulactone	-3438	PHE-121	1
25.		Geranial	-3278	THR-690, SER-689	2
26.		Citronelal	-3946	GLU-315, PHE-121	2
27.		Sabinene	-3886	GLU-315	1
28.		Beta-pine	-3858	HIS-96	1
29.	**2E4UA**	Linalool	-3636	ARG-114	1
30.		Neral	-3772	THR-190	1
31.		Sulactone	-3346	PHE-652	1
32.		Geranial	-3876	GLU-763	1
33.		Citronelal	-3976	THR-752	1
34.		Sabinene	-3904	SER-452	1
35.		Beta-pine	-3844	TRP-782	1

As per the docking results it is seen that the receptors 7JVRA, 3U7UA, 71DDA, 6MMPD, 2E4UA docks with the phytocompounds of the ayurvedic medicinal plants viz. *Withania sominefera, Melisa officinalis, Piper methysticum, Veleriana officinalis* and *Hypericum perforatum* with a good docking score and interactions.

Table 9. Piper methysticum

SL. NO	RECEPTOR (PROTEIN)	COMPOUND	DOCKING SCORE (-Kcal/mol)	INTERACTING AMINO ACID	NO OF INTERACTION
1.	**7JVRA**	5-hydroxy-4–7-dimethoxy	-4620	SER285, LEV284, LYS362	3
2.		Matteacinol	-4600	LEU284, SER285	2
3.		Tetrahydro yangonin	-4528	LFU284, SER285	2
4.		yangonin	-4196	ASN224, LYS5362	2
5.	**3U7UA**	5-hydroxy-4–7-dimethoxy	-4222	ASN-363, SER310	2
6.		Matteacinol	-3982	CYS-625	1
7.		Tetrahydro yangonin	-4020	ASN253	1
8.		yangonin	-3946	PHE247	1
9.	**71DDA**	5-hydroxy-4–7-dimethoxy	-3960	ARG-91, TYR-288, THR-289	3
10.		Matteacinol	-3864	SER-112, ARG-126, SER-206, TYR-288	4
11.		Tetrahydro yangonin	-3998	TYR-89, SER-112, PHE-113	3
12.		yangonin	-3954	ASP-322, VAL-329	2
13.	**6MMPD**	5-hydroxy-4–7-dimethoxy	-4522	PRO-330	1
14.		Matteacinol	-4478	HIS-332, PHE-121	2
15.		Tetrahydro yangonin	-4292	GLY-129, TYR-281	2
16.		yangonin	-4912	PHE-121	1
17.	**2E4UA**	5-hydroxy-4–7-dimethoxy	-4988	ARG-114, THR-118, ASP-121	3
18.		Matteacinol	-4532	ILE-453, THR-190	2
19.		Tetrahydro yangonin	-4844	GLY-611	1
20.		yangonin	-4428	GLY611	1

Table 10. Veleriana officinalis

SL. NO	RECEPTOR (PROTEIN)	COMPOUND	DOCKING SCORE (-Kcal/mol)	INTERACTING AMINO ACID	NO OF INTERACTION
1.	**7JVRA**	Valerenic acid	-4204	LEU-284, GLN-365	2
2.		Isovaleric acid	-2604	GLU282, GLU280, ARG230	3
3.		Boryal acetate	-3522	SER-285	1

(*continued*)

Table 10. (*continued*)

SL. NO	RECEPTOR (PROTEIN)	COMPOUND	DOCKING SCORE (-Kcal/mol)	INTERACTING AMINO ACID	NO OF INTERACTION
4.		valerianol	-3976	GLN-365	1
5.		Myrtenyl acetate	-3712	ARG-220, GLN-365	2
6.	**3U7UA**	Valerenic acid	-3576	THR-84	1
7.		Isovaleric acid	-2510	PRO-331	1
8.		Boryal acetate	-3140	ARG-106	1
9.		valerianol	-3520	CYS-593	1
10.		Myrtenyl acetate	-3206	CYS-611	1
11.	**71DDA**	Valerenic acid	-3604	ASP-116, THR-117	2
12.		Isovaleric acid	-2218	SER-582, GLN-581	2
13.		Boryal acetate	-3442	ASP-152	1
14.		valerianol	-4048	SER-206	1
15.		Myrtenyl acetate	-3400	GLN-159, ASP-116	2
16.	**6MMPD**	Valerenic acid	-4100	SER-689	1
17.		Isovaleric acid	-2722	HIS-332	1
18.		Boryal acetate	-3656	ILE-134	1
19.		valerianol	-4076	HIS-96	1
20.		Myrtenyl acetate	-3846	ASP-731	1
21.	**2E4UA**	Valerenic acid	-2734	SER-610	1
22.		Isovaleric acid	-2720	SER-625	1
23.		Boryal acetate	-3990	ASN-137	1
24.		valerianol	-3982	MET-463	1
25.		Myrtenyl acetate	-3938	ALA-133, GLU-122	2

Table 11. Hypericum perforatum

SL. NO	RECEPTOR (PROTEIN)	COMPOUND	DOCKING SCORE (-Kcal/mol)	INTERACTING AMINO ACID	NO OF INTERACTION
1.	**7JVRA**	Caryophyllene oxide	-4276	ASN-224	1
2.		Spathulenol	-4016	GLN-277	1
3.		1-Hexanol	-4954	ARG-220, ASN-224	2
4.	**3U7UA**	Caryophyllene oxide	-3088	TYR-52	1
5.		Spathulenol	-3362	ASN-253	1
6.		1-Hexanol	-4344	CYS-625	1
7.	**71DDA**	Caryophyllene oxide	-3640	ASN-805, SER-802	2
8.		Spathulenol	-3584	THR-289	1
9.		1-Haxanol	-4406	GLU-207, SER-206, PHE-113, SER-112	4
10.	**6MMPD**	Caryophyllene oxide	-3758	SER-132, TYR-281	2
11.		Spathulenol	-3774	LYS-453	1
12.		1-Haxanol	-4694	TYR-730	1
13.	**2E4UA**	Caryophyllene oxide	-3830	CYS-30	1
14.		Spathulenol	-3798	SER-810	1
15.		1-Haxanol	-5148	ARG-465, ASN-395	2

4 Conclusion

As per docking result it is seen that the phytocompounds Lutolin, Kaemferol, Ginkolide A, Ascorbic asid, Tetrahydroyangonin, Matteacinol, 5-hydroxy-4–7-dimethoxy, Tetrahydro yangonin, D-Allose and Azetidine docks with all the receptors. Hence these compounds can be successfully considered as ligands for the receptors on further validation using in-vitro and in-vivo studies.

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