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Research Article

Establishing a Remedy for Phenylketonuria Disease from Indian Ayurvedic Herbs

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ABSTRACT

The phenylketonuria (PKU) disease is an inherited disorder that increases the levels of a substance called phenylalanine in the blood and if not treated, phenylalanine can build up to harmful levels in the body. People with this disorder can't break down the amino acid phenylalanine. This phenylalanine, then builds up in the blood and brain causing intellectual disability and other serious health problems. It is rare but a serious inherited disorder. The main objective of this study is to establish a remedy for the phenylketonuria disease (novel drug leads for phenylketonuria disease's receptors viz. ASCL1 gene (achaete-scute family bHLH transcription factor 1), GCH1 gene (GTP cyclohydrolase 1) and MAOB (Monoamine Oxidase B)) using phytocompounds from ayurvedic herbs. To achieve this objective we performed virtual screening with phytocompounds from ayurvedic herbs against the phenylketonuria disease's receptors followed by ADME studies on the phytocompounds selected by virtual screening. Based on the analysis of the results of virtual screening and subsequent ADME studies on the phytocompounds it is seen that curcumin can be successfully considered as novel drug lead for treating phenylketonuria disease.

Keywords: *Phenylketonuria*; ADME; ASCL 1 gene; GHC1 gene; MAOB gene; Modeling; Docking

INTRODUCTION

Phenylketonuria which is commonly known as PKU, is an inherited disorder that increases the levels of phenylalanine (which is a building block of proteins) in the blood that is obtained through the diet (it is found in all proteins and in some artificial sweeteners) [1-3]. If PKU is not timely treated, phenylalanine can build up to harmful levels of toxins in the body, causing brain damage. The U.S. Food and Drug Administration (FDA) has approved the drug sapropterin dihydrochloride (Kuvan®) for the treatment of PKU. Kuvan® is a form of BH4, which is a substance in the body that helps break down phenylalanine [4-6]. PKU is caused by mutations in the gene PAH, GCH1, MAOB, ALB, IGF1, ASCL1, among others Koch et al., Moyle et al., Naz and John. PKU`s symptoms include seizures, tremors or trembling and shaking, stunted growth, hyperactivity, skin conditions such as eczema, a musty odor (bad smell) in their breath, skin or urine. Infants with classic PKU appear normal until they are a few months old and without treatment, these children develop permanent intellectual disability. Children with PKU usually have lighter skin and hair than unaffected family members and more prone to have skin disorders like eczema [1-9].

Genes considered in this work

Classical PKU is an autosomal recessive disorder caused by mutations in both alleles of the gene coding for phenylalanine hydroxylase found on chromosome 12.

ASCL1 gene (achaete-scute family bHLH transcription factor 1)

It encodes a member of the basic helix- loop-helix (BHLH) family of transcription factors, a protein that activates transcription by binding to the E box (5'- CANNTG-3'). Dimerization with other BHLH proteins is required for efficient DNA binding and this protein plays a role in the neuronal commitment and differentiation and in the generation of olfactory and autonomic neurons. Mutations in this gene cause the congenital central hypoventilation syndrome (CCHS) phenotype in rare cases [10].

GCH1 gene (GTP cyclohydrolase 1)

It provides instructions for making an enzyme called GTP cyclohydrolase 1, which is involved in the first of three steps in the production of a molecule called tetrahydrobiopterin (BH4). Other

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enzymes help to carry out the second and third steps in this process. Tetrahydrobiopterin plays a significant role in processing several protein building blocks (amino acids) in the blood; specifically, tetrahydrobiopterin, which is involved in the production of two neurotransmitters called dopamine and serotonin. Among their many functions, dopamine spreads signals within the brain to produce smooth physical movements and serotonin regulates mood, emotion, sleep, and appetite. Since it helps enzymes carry out chemical reactions, tetrahydrobiopterin is known as a cofactor [11].

MAOB (Monoamine oxidase B)

The protein coded by this gene belongs to the flavin monoamine oxidase family and it is an enzyme located in the mitochondrial outer membrane. It catalyzes the oxidative deamination of biogenic and xenobiotic amines and plays an important role in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues. This protein preferentially degrades benzylamine and phenylethylamine [12].

Ayurvedic herbs used and their active components

- **Wood betony:** The principal chemical components present in this plant are Tannins, Betulinic acid, oleonilic acid, rosamarinic acid, rutin, urosolic acid, stachydrine and glycosides.
- **Nettle:** The principal chemical components present in this plant are histamine, formic acid, acetylcholine, serotonin and vitamins.
- **Plantago ovate**: The principal chemical components present in this plant are xylose, arabinose, alanine, valine, glutamic acid, glycine, cysteine, lysine, leucine, tyrosine and xylose.
- **Turmeric:** The principal chemical components present in this plant are curcumin and camphene.
- **Dandelion:** The principal chemical components present in this plant are taraxacin, laevulin, resin and inulin.

The main objective of this study is to establish a novel ligand as drug for the PKU from the phytocompounds of the above mentioned ayurvedic herbs.

METHODOLOGY

The proteins corresponding to the genes for the PKU were downloaded from Genbank database and their 3d structures were modeled using modeller [1,13]. Modeller is used for homology or comparative modeling of protein three-dimensional structures wherein the user provides an alignment of a sequence to be modeled with known related structures and modeller automatically calculates a model containing all non-hydrogen atoms [13]. The modeller generated models were verified using Ramachandran Plot [1,14]. Ramachandran Plot is a way to visualize energetically allowed regions for backbone dihedral angles ψ against φ of amino acid residues in protein structure [14]. The 3d structures of the phytocompounds mentioned above were downloaded from pubchem database. These compounds were docked with the PKU receptors using PATCHDOCK server which is a server for molecular docking [1,15]. ADME studies were done with the phytocompounds which showed best docking results with the PKU receptors [1,16,17]. ADME is "absorption, distribution, metabolism, and excretion" which is the disposition of a pharmaceutical compound within an organism. This is based on Lipinski's rule of five to evaluate drug-likeness or determine if a chemical compound with a certain pharmacological or biological activity has chemical properties and physical properties that would make it a likely orally active drug in humans [17].

RESULT AND DISCUSSION

Homology modelling

PKU (phenylketonuria) gene receptors were retrieved from GENBANK database Table 1. The homologous templates of the receptors in Table 1 were selected using BLAST search against Protein Data Bank (PDB) and the selected templates were downloaded from PDB Table 2A-C. Using Modeller, the 3d structures of the receptors in Table 1 were modelled [13]. The models were verified using Rampage Ramachandran Plot server Table 3A-C and Figure 1A-C [14].

Docking

The selected models in Table 3 were docked with the phytocompounds from the Ayurvedic herbs using PATCHDOCK [15]. The docking scores were noted in Table 4A1-A5, B1-B5 and C1-C5. As per the virtual screening studies we find the phytocompounds betulinic acid, rutin, lecithin and curcumin docks with all the receptor genes. Hence we take these phycompounds into consideration (in comparison with the others used in this work) for further ADME studies to see which of these compounds show NO violations in the Lipinski rule of 5 (Figure 2A-C).

Table 1: PKU genes with Genbank accession number.

Serial No.	Receptor Name	Code	Accession Number
1	Achaete-scute family bHLH transcription	ASCL1	P50553.2
2	GTP cyclohydrolase	GCH1	P30793.1
3	Monoamine oxidase B	MAOB	P27338.3

Table 2(A): Homologous template of ASCL1.

Accession	Query cover	Identity
2QL2 B	22%	45%
4AYA A	22%	41%
2YPAB*	64%	33%

Homologous template search by https://toolkit.tuebingen.mpg.de/#/tools/hhpred since BLAST generated two homologous templates [18]

Table 2(B): Homologous template of GCH 1.

Accession	Query cover	Identity
1IS7 A	92%	93%
1FB1 A	78%	100%
1WM9 A	74%	58%

Table 2(C): Homologous template of MAOB.

Accession	Query cover	Identity
1GOS A	100%	100%
2C73 A	100%	99%
2BK4 A	100%	99%

Table 3(A-C): Ramachandran Plot Analysis of modeler generated models.

ASCL1				
	Number of residues in favored region (~98.0% expected)	**Number of residues in allowed region (~2.0% expected)**	**Number of residues in outlier region**	
Model 1	184 (96.3%)	5 (2.6%)	2 (1.0%)	
Model 2	178 (93.2%)	7 (3.7%)	6 (3.1%)	
Model 3	177 (92.7%)	12 (6.3%)	2 (1.0%)	
Model 4	181 (94.8%)	8 (4.2%)	2 (1.0%)	
Model 5	185 (96.9%)	5 (2.6%)	1 (0.5%)	Selected
Model 5 is selected as the best model since it has highest number of residues in the favored region and least number of residues in the outlier region.				

Table 3(B)

GCH1				
	Number of residues in favored region (~98.0% expected)	**Number of residues in allowed region (~2.0% expected)**	**Number of residues in outlier region**	
Model 1	235 (94.8%)	7 (2.8%)	6 (2.4%)	
Model 2	241 (97.2%)	5 (2.0%)	2 (0.8%)	Selected
Model 3	239 (96.4%)	7 (2.8%)	2 (0.8%)	
Model 4	237 (95.6%)	8 (3.2%)	3 (1.2%)	
Model 5	239 (96.4%)	9 (3.6%)	0 (0.0%)	
Model 2 is selected as the best model since it has highest number of residues in the favored region				

Table 3 (C)

MAOB			
	Number of residues in favored region (~98.0% expected)	**Number of residues in allowed region (~2.0% expected)**	**Number of residues in outlier region**
Model 1	507(97.9%)	9(1.7%)	2(0.4%) Selected
Model 2	506(97.7%)	10(1.9%)	2(0.4%)
Model 3	506(97.7%)	10(1.9%)	2(0.4%)
Model 4	505(97.5%)	11(2.1%)	2(0.4%)
Model 5	506(97.7%)	10(1.9%)	2(0.4%)
Model 1 is selected as the best model since it has highest number of residues in the favored region			

Table 4 (A1): Docking results of ASCL1 receptor with compounds from Wood Betony.

WOOD BETONY					
Sl.no	**Receptor**	**Ligand**	**Docking score (kcal/mol)**	**No. of interactions**	**Interacting amino acids**
1	ASCL1	Betulinic acid	5640	5	ASP-110
2	ASCL1	Delphinic acid	2190	1	SER-177 SER-144 GLU-182 TYR-193
3	ASCL1	Oleonilic acid	5524	1	PRO-143
4	ASCL1	Rosamarinic acid	4642	2	SER-148
5	ASCL1	Rutin	5540	6	GLU-180
					VAL-112 ALA-111 ASP-110 SER-156

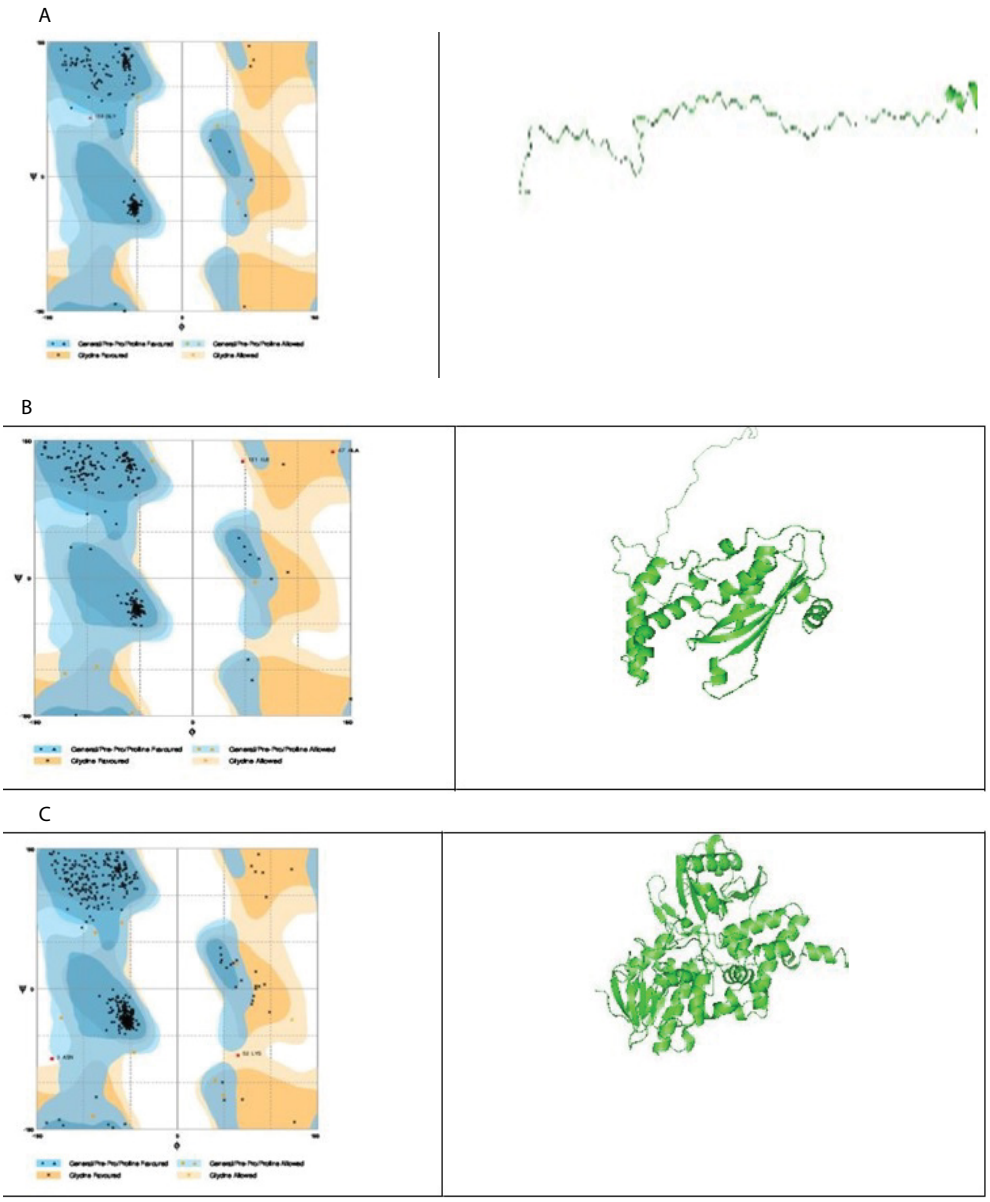

Figure 1A: Ramachandran plot analysis of the best model (5) of ASCL1 receptor.

Figure 1B: Ramachandran plot analysis of the best model (2) of GCH1 receptor.

Figure 1C: Ramachandran plot analysis of the best model (1) of MAOB receptor.

Table 4 (A2): Docking results of ASCL1 receptor with compounds from NETTLE.

NETTLE					
Sl.no	Receptor	Ligand	Docking score (kcal/mol)	No. of interactions	Interacting amino acids
1	ASCL1	Histamine	2130	1	TYR-193
2	ASCL1	Formic acid	1190	2	ARG-100 GLY-132
3	ASCL1	Acetylcholine	2778	1	ARG-131
4	ASCL1	Serotonin	3202	3	LYS-85 GLN-71 ARG-74

Table 4 (A3): Docking results of ASCL1 receptor with compounds from PLANTAGO OVATO.

PLANTAGO OVATO					
Sl.no	Receptor	Ligand	Docking score (kcal/mol)	No. of interactions	Interacting amino acids
1	ASCL1	Arabinose	2182	3	ARG-74
2	ASCL1	Xylose	2360	4	LEU-86 LYS-88 LEU-86
3	ASCL1	Valine	2192	1	ARG-74 LYS-84 LYS-88 ASN-67
4	ASCL1	Alanine	1876	2	GLY-132
5	ASCL1	Glutamic acid	2280	4	ARG-100 LYS-88
6	ASCL1	Glycine	1582	3	GLN-71 ASN-67 ARG-74 ARG-100
7	ASCL1	Cysteine	1996	1	GLY-132 GLU-90 ARG-131
8	ASCL1	Lysine	2704	2	ALA-179 ASP-110
9	ASCL1	Leucine	2370	2	ARG-74 ASN-67
10	ASCL1	Tyrosine	2970	2	SER-148 ASP-110
11	ASCL1	Rhamnose	2418	3	ASN-67 LYS-88 ARG-74

Table 4 (A4): Docking results of ASCL1 receptor with compounds from TURMERIC.

TURMERIC					
Sl.no	Receptor	Ligand	Docking score (kcal/mol)	No. of interactions	Interacting amino acids
1	ASCL1	Curcumin	5016	5	VAL-125 ARG-126 SER-128 ALA-129 PRO-127
2	ASCL1	Camphene	2862	0	

Table 4 (A5): Docking results of ASCL1 receptor with compounds from DANDELION.

DANDELION					
Sl.no	Receptor	Ligand	Docking score (kcal/mol)	No. of interactions	Interacting amino acids
1	ASCL1	Taraxacin	3922	2	SER-148 GLU-180
2	ASCL1	Laevulinic acid	2098	2	GLY-81 ARG-131
3	ASCL1	Choline	2160	2	ARG-131 ARG-100
4	ASCL1	Lecithin	6648	9	GLY-119 ARG-121 ALA-117 LEU-116 ASP-110 ALA-111 GLU-180 ALA-179 SER-144

Table 4 (B1): Docking results of GCH1 receptor with compounds from WOOD BETONY

WOOD BETONY					
Sl.no	**Receptor**	**Ligand**	**Docking score (kcal/mol)**	**No. of interactions**	**Interacting amino acids**
1	GCH1	Betulinic acid	4608	5	TRP-53 GLU-56
2	GCH1	Delphinic acid	2142	2	LYS-54 GLY-55 ARG-57 ALA-120 ILE-121
3	GCH1	Oleonilic acid	4708	1	HIS-210
4	GCH1	Rosamarinic acid	4260	4	ILE-113 TYR-175 TYR-109 GLU-56
5	GCH1	Rutin	5020	6	GLY-55 GLU-56 ILE-113 TYR-175 ARG-178 TYR-109
6	GCH1	Urosolic acid	4992	5	ARG-178 PRO-58 ARG-57 GLY-55 GLU-56
7	GCH1	Stachydrine	2524	3	LEU-117 ILE-121 ALA-120

Table 4(B2): Docking results of GCH1 receptor with compounds from NETTLE.

NETTLE					
Sl.no	**Receptor**	**Ligand**	**Docking score (kcal/mol)**	**No. of interactions**	**Interacting amino acids**
1	GCH1	Histamine	2208	3	ASN-118 ALA-120 ILE-121
2	GCH1	Formic acid	1042	1	LEU-163
3	GCH1	Acetylcholine	2578	1	THR-112
4	GCH1	Serotonin	2806	0	

Table 4(B3): Docking results of GCH1 receptor with compounds from PLANTAGO OVATO.

PLANT OVAGATO					
Sl.no	**Receptor**	**Ligand**	**Docking score (kcal/mol)**	**No. of interactions**	**Interacting amino acids**
1	GCH1	Arabinose	2158	1	ALA-196
2	GCH1	Xylose	2182	1	HIS-210
3	GCH1	Valine	2164	1	GLN-161
4	GCH1	Alanine	1772	1	ILE-121
5	GCH1	Glutamic acid	2152	3	ILE-121 ALA-196 GLN-161
6	GCH1	Glycine	1462	1	GLU-124
7	GCH1	Cysteine	1930	1	GLN-161
8	GCH1	Lysine	2490	1	TYR-109

9	GCH1	Leucine	2410	4	LEU-117 ASN-118 ALA-120 ILE-121
10	GCH1	Tyrosine	2794	4	ASP-119 ASN-118 ALA-196 ILE-121
11	GCH1	Rhamnose	2282	4	LEU-117 ASN-118 ALA-120 ILE-121

Table 4(B4): Docking results of GCH1 receptor with compounds from TURMERIC.

TURMERIC					
Sl.no	**Receptor**	**Ligand**	**Docking score (kcal/mol)**	**No. of interactions**	**Interacting amino acids**
1	GCH1	Curcumin	4332	6	GLY-55 GLU-56 SER-60 PRO-58 ARG-57 ARG-178
2	GCH1	Camphene	2696	0	

Table 4(B5): Docking results of GCH1 receptor with compounds from DANDELION.

DANDELION					
Sl.no	**Receptor**	**Ligand**	**Docking score (kcal/mol)**	**No.of interactions**	**Interacting amino acids**
1	GCH1	Taraxacin	3368	2	GLU-183 HIS-144
2	GCH1	Laevulinic acid	2026	3	GLN-161 ALA-196 LEU-117
3	GCH1	Choline	2128	0	
4	GCH1	Lecithin	6712	6	LEU-165 LEU-163 TYR-156 GLU-124 HIS-126 SER-250

Table 4(C1): Docking results of MAOB receptor with compounds from WOOD BETONY.

WOOD BETONY					
Sl.no	**Receptor**	**Ligand**	**Docking score (kcal/mol)**	**No. of interactions**	**Interacting amino acids**
1	MAOB	Betulinic acid	5148	4	TYR-112 THR-479 GLU-483 ASP-123
2	MAOB	Delphinic acid	2608	1	GLY-13
3	MAOB	Oleonilic acid	5508	2	THR-478 GLU-483
4	MAOB	Rosamarinic acid	5362	2	TYR-393 ARG-36

5	MAOB	Rutin	5034	7	THR-478 ILE-477 ARG-120 ARG-127 ARG-484 ASN-116 THR-480
6	MAOB	Urosolic acid	5442	3	GLU-483 ILE-477 TYR-112
7	MAOB	Stachydrine	2936	1	GLN-206

Table 4(C2): Docking results of MAOB receptor with compounds from NETTLE.

NETTLE					
Sl.no	**Receptor**	**Ligand**	**Docking score (kcal/mol)**	**No. of interactions**	**Interacting amino acids**
1	MAOB	Histamine	2674	0	
2	MAOB	Formic acid	1360	2	TYR-326 ILE-199
3	MAOB	Acetylcholine	3552	0	
4	MAOB	Serotonin	3786	2	TYR-60 SER-59

Table 4(C3): Docking results of MAOB receptor with compounds from PLANTAGO OVATO.

PLANTAGO OVATO					
Sl.no	**Receptor**	**Ligand**	**Docking score (kcal/mol)**	**No. of interactions**	**Interacting amino acids**
1	MAOB	Arabinose	2508	3	SER-394 GLY-13 ARG-36
2	MAOB	Xylose	2740	2	GLN-206 TYR-435
3	MAOB	Valine	2682	2	GLU-34 TYR-393
4	MAOB	Alanine	2188	1	VAL-235
5	MAOB	Glutamic acid	2850	2	GLU-34 ALA-263
6	MAOB	Glycine	1798	3	ALA-429 THR-428 ARG-415
7	MAOB	Cysteine	2364	1	VAL-235
8	MAOB	Lysine	3284	0	
9	MAOB	Leucine	2822	2	TYR-393 GLU-34
10	MAOB	Tyrosine	3624	2	ARG-42 TYR-393
11	MAOB	Rhamnose	2748	2	TYR-393 ARG-36

Table 4(C4): Docking results of MAOB receptor with compounds from TURMERIC.

TURMERIC					
Sl.no	**Receptor**	**Ligand**	**Docking score (kcal/mol)**	**No. of interactions**	**Interacting amino acids**
1	MAOB	Curcumin	5900	4	ARG-42 ALA-439 GLU-34 ILE-264
2	MAOB	Camphene	3148	1	TYR-398

Table 4(C5): Docking results of MAOB receptor with compounds from DANDELION.

DANDELION					
Sl.no	**Receptor**	**Ligand**	**Docking score (kcal/mol)**	**No. of interactions**	**Interacting amino acids**
1	MAOB	Taraxacin	4340	2	GLN-206 CYS-172
2	MAOB	Laevulinic acid	2646	3	CYS-172 TYR-435 TYR-188
3	MAOB	Choline	2640	0	
4	MAOB	Lecithin	6636	5	ASP-132 GLN-464 SER-465 PRO-467 GLU-466

Table 5: ADME screening.

ADME Screening						
Ligands	**miLogP**	**TPSA**	**Natoms**	**MW**	**volume**	**n violations**
Acetylcholine	-3.56	26.3	10	146.21	156.67	0
Alanine	-2.69	63.32	6	89.09	84.31	0
Arabinose (Oxane-2,3,4,5-tetrol)	-2.22	90.15	10	150.13	126.96	0
Betulinic acid (Lup-20(29)-en-28-oic acid, 3beta-hydroxy-)	7.04	57.53	33	456.71	472.04	1
Camphene	3.33	0	10	136.24	152.37	0
Choline	-4.24	20.23	7	104.17	120.16	0
Curcumin	2.3	93.07	27	368.38	332.18	0
Cysteine	-2.71	63.32	7	121.16	102.22	0
Delphinic acid (Isovaleric acid)	1.21	37.3	7	102.13	106.39	0
Formic acid	-0.51	37.3	3	46.02	39.64	0
Glutamic acid	-3.25	100.62	10	147.13	128.36	0
Glycine	-2.55	63.32	5	75.07	67.73	0
Histamine	-0.85	54.71	8	111.15	109.77	0
Lecithin	2.69	101.97	44	643.89	668.3	1
Leucine	-1.38	63.32	9	131.18	134.5	0
Levulinic acid	-0.35	54.37	8	116.12	108.78	0
Lysine	-3.18	89.34	10	146.19	146.25	0
Oleanoic acid	6.72	57.53	33	456.71	471.14	1
Rhamnose (6- Methyloxane-2,3,4,5- tetro)l	-1.64	90.15	11	164.16	143.55	0
Rosmarinic acid (Rosmarinsaure)	1.63	144.52	26	360.32	303.54	0
Rutin (Vitamin P	-1.06	269.43	43	610.52	496.07	3
Serotonin	0.57	62.04	13	176.22	165.93	0
Stachydrine	-5.31	40.13	10	143.19	142.62	0
Taraxacin	2.56	43.38	18	242.27	220.04	0
Tyrosine	-1.71	83.55	13	181.19	163.98	0
Urosolic acid (Carissic acid)	6.79	57.53	33	456.71	471.49	1
Valine	-1.91	63.32	8	117.15	117.7	0
Xylose (Ribose, D)	-2.22	97.98	10	150.13	130.97	0

Figure 2A: ASCL1 docking images.

Figure 2B: GCH1 docking images.

Figure 2C: MAOB docking images.

ADME

The phytocompounds used in this work are subjected to ADME screening using molinspiration server [16-18]. The results are noted in Table 5 [1]. From the above table it is seen that the compounds betulinic acid, rutin and lecithin have 1, 3 and 1 violations respectively. Compound curcumin successfully clears ADME studies as it shows NO violations in the Lipinski rule of 5.

CONCLUSION

As per the virtual screening studies we find the phytocompounds betulinic acid, rutin, lecithin and curcumin docks with all the receptor genes. As per ADME studies compounds betulinic acid, rutin and lecithin cannot be considered as drug lead as they show 1, 3 and 1 violation respectively in ADME studies (as per Table 5). Compound curcumin successfully clears ADME studies (as per Table 5, there are no violations in the ADME properties of curcumin and hence the compound curcumin can be successfully considered as novel drug for phenylketonuria disease.

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