In silico Determination of Plant Compounds in the Treatment of Hemochromatosis- A Hereditary Genetic Iron Disorder Syndrome

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Abstract : Hemochromatosis is a hereditary defect are the patient's incapability to prevent the excess iron entering the bloodstream and accumulates in parenchymatous organs. It was identified that the loss of gene responsible for the enzyme hepcidin, an iron hormone produced in the liver results in paradigmatic iron-loading disorder. India has a vast diversity of plants, perhaps from our ancient times medicinal plants have a significant role in maintaining the health. Utilization of medicinal plants in the field of medicine has been appreciated by World Health Organization (WHO) and 80% of human population are depend in the developing countries. The present study focused on plants like *Aeridescrispum*, *Aeridesodoratum*, *Agrostophyllum callosum*, *Arundinagramnifolia*, *Bulbophyllumodoratissimum*, *Cephalantheropsisgracilis*, *Coelogynecristata*, *Dendrobiumnobile*, *Eulophianuda*, *Gastrodiaelata* and *Habenariarepens* and their phytochemical compounds reported to be present are retrieved from the PubChem database. The *in silico* techniques were utilized to analyze the compounds for its absorption, distribution, metabolism and excretion property as well as its efficiency in interacting with the target protein of PDB ID: 1M4E. The docking study was determined using Glide module of Schrodinger software and it was observed that the compound moscatilin had significant G.score and interaction with the protein.

Keywords–Hemochromatosis, Medicinal Plants, Defective Hepcidin, Docking studies, Moscatilin**.**

I. INTRODUCTION

Hemachromatosis was first described by a German pathologist in 1889[1], is a hereditary disorder defines the failure of body system to excrete the excess iron which eventually damage tissues and organs. It is also called an iron overload disorder. Normal iron content in the body is 3-4 g and are expelled out of body through stool, sweat and via shed skin cells. Iron overloaded diseases are frequently associated with hereditary defects or secondary disturbances of iron metabolism that results from excessive blood transfusion, iron supplementation or iron injections. Iron functions mainly in carrying oxygen to organs and tissues, whereas extra iron are stored in the joints and organs like liver, heart and pancreas. The symptoms include tiredness, joint pain, abdominal pain, weight loss as early indications, whereas in severe conditions it may develop as arthritis, liver disease, diabetes, heart abnormalities and skin discoloration. There are four types of hereditary hemochromatosis, Type 1, 2, 3 and 4 where the classification depends on age and the genetic cause as well as mode of inheritance[2]. The iron overload also has its own implications where this condition may cause damage internal organs and causes risks of diabetes, heart attack and cancer among the elderly population, whereas in the hereditary hemochromatosis is observed to prevail among younger generation[8].

Hepcidin is a regulator protein(25-amino acid length peptide) for iron absorption which was produced by hepatocytes[3]. The level of hepcidin expression leads to either anemia at increased level[4] or hemochromatosis at lesser level[5].Hemochromatosis are mainly due to the hepcidin deficiency and/or altered ferroportin (a membrane iron export channel protein)[6]. Hepcidin regulates the intestinal iron absorption and maternal-fetal iron transport[3]. Iron has its role in energy metabolism, DNA replication, oxygenating blood cells and haemoglobin, converting food to energy, maintain normal immune system and normalize cognitive function. Iron is a redox element and act as indispensable cofactor for enzymes such as helicases, nucleases, glycosylases, demethylases[7] (Puig*et al.*, 2017).Abbaspour et al., (2014)[8] has reviewed the iron metabolism and bioavailability, iron requirement, consequences and causes of iron deficiency.

According to WHO, most of the developing and developed countries rely on the herbal based products due to its safety and its medicinal ability, the current study postulates to observe the efficiency of the plant secondary molecules from *Dendrobiumnobile, Aeridesodoratum, Arundinagramnifolia, Gastrodiaelata, Cephalantheropsisgracilis, Eulophianuda, Coelogynecristata, Agrostophyllum callosum, Bulbophyllumodoratissimum, Malaxismucifera, Habenariarepens*and*Aeridescrispum.*

II. MATERIALS AND METHODS

The 3D structure of protein hepcidin was retrieved from the PDB of corresponding ID: 1M4E (http:/www.rcsb.org/pdb/home/home.do).The active site pocket for the protein was predicted using Ligsite, an online tool available at http:/projects.biotec.tu-dresden.de/pocket/.The plant molecules are retrieved from PubChemdatabase, a database specifically for small molecules. The pubchem compounds were retrieved in .sdf file format.The ADME properties were analyzed for each compound to analyze its drug-likeness using Qikprop, a Schrodinger module. The compounds obeying ADME properties are further taken for docking studies. The docking was carried out in Glide module of Schrodinger software. In Glide, the protein was prepared by removing the unwanted water molecules and the energy was minimized. The structure was optimized before utilized for docking. The small molecules were also prepared for neutralizing charged groups, tautomerized and improved chirality. The interactions were observed in the software PyMol viewer. Finally, the potential of compounds to interact with the protein was carried out using glide module and hydrogen bond interactions were observed using Pymol software.

III. RESULTS AND DISCUSSION

The plant compounds were observed for ADME properties and the obtained results were tabulated (Table 3.1). ADME properties of the molecule were observed to be in the specified range. The molecular weight, surface area solvent accessibility (SASA), hydrogen donor and acceptor bond, octanol/water coefficient, blood/brain barrier, metabolic involvement, percent human oral absorption were analyzed. Most of the compounds indicated the higher percentage for human oral absorption. Lupeol and myricetin had violated the Lipinski's rule of five. Therefore, all the compounds were further subjected for docking studies to observe the interaction type with the target protein. The docking results were observed for Glide score (G.score), interacting residues and bond length (Table 3.2).

The Glide score were observed in the range of -2 to -6 Kcal/mol. The compound moscatilin from *Dendrobiumnobile* showed -6.43 Kcal/mol of G.score and the formed 4 number of hydrogen bonds with the residues Cys5, Lys13, Met16. The compound had two hydrogen bond interaction with Met16 of bond length 1.7 and 2.3Å, whereas Cys5 and Lys13 had bond length of 2.0 and 2.2Å, respectively. The compound 1,8 cineole of *D. nobile* and gallic acid of *Aeridesodoratum*showed G.score of -5.74 and -5.04Kcal/mol. Former compound 1,8 cineole had 5 hydrogen bond interaction where single interaction was observed with Lys19, Met16, Lys13 and two bonds formed with Arg11 and the respective bond lengths were observed to be2.0, 2.1, 1.9, 2.5 and 1.8Å. The compound gallic acid had 4 interactions where each residues had two bond formation and the bond lengths were observed to be 2.5, 1.8, 2.1 and 1.8Å, respectively. The compounds gigantol from *D. nobile*, syringic acid, catechin, caffeic acid, quercetin, apigenin and myricetin from *A. odoratum*, gastrodin from *Gastrodiaelata*, cis-ferulic acid from *Cephalantheropsisgracilis*, vanillic acid from *Arundinagramnifolia*, and habenariol from *Habenariarepens* had G.score in the range of -4Kcal/mol. The interaction of moscatilin alone was shown in the figure 3.1.

Table 3.1: ADME PROPERTIES OF PLANT COMPOUNDS

Molecule	Molecular Weight	SASA	Donor-Hydrogen Bond	Acceptor-Hydrogen Bond	QPlog P for water/gas	QPlog P for octanol/water	QPlog BB for brain/blood	#metab	Human Oral Absorption	Percent Human Oral Absorption	Lipinski Rule of Five	Jorgensen Rule Of Three
Normal range	**130.0 - 725.0**	**300.0 - 1000.0**	**0.0 - 6.0**	**2.0 - 20.0**	**4.0 - 45.0**	**-8.5**	**-4.2**	**1.0 - 8.0**	**1,2 or 3 for low, medium or high**	**(<25% is poor) (>80% is high)**	**Max.4**	**Max.3**
Gallic acid	170.1	342.4	4	4	12	-0.6	-1.7	3	2	41.5	0	1
Vanillin	152.1	353.7	1	4	6.5	1	-0.7	2	3	82	0	0
Isatin	147.1	330	1	5	8.7	0.1	-0.6	1	2	73.6	0	0
Vanillic acid	168.1	360.2	2	4	8.1	1	-0.9	2	2	67	0	0
Syringaldehyde	182.2	393.3	1	4	6.7	0.4	-0.7	3	3	78.9	0	0
Syringic acid	198.2	400	2	4	8.4	1	-1	3	3	66.7	0	0
Vanillyl alcohol	154.2	361.6	2	3	7.3	0.7	-0.5	3	3	84.4	0	0
Catechin	290.3	509.5	5	5	15.6	0.5	-1.8	7	2	61	0	1
Indole 3 carboxylic acid	230.3	459.6	3	4	10.6	-0.3	-0.2	3	2	53.3	0	0
Tryptanthin	248.2	462.3	0	6	9.9	1	-0.4	1	3	84.6	0	0
Gastrodin	286.3	509.5	5	11	19.4	-1	-1.9	5	2	55.7	0	0
Nudol	270.3	491.2	2	3	8.2	2.7	-0.6	4	3	96.9	0	0
Moscatilin	304.3	577.6	2	4	7.7	3.5	-0.7	7	3	100	0	1
Orchinol	256.3	501.3	1	2	5.5	3.5	-0.1	5	3	100	0	0
Lupeol	426.7	737	1	2	4.6	5.3	0.1	3	1	100	1	1
Bulbophyllanthrone	314.3	522.9	1	7	10.4	1.4	-0.9	4	3	81.9	0	0

Dendrobine	263.4	490	0	5	5.9	1.8	0.5	2	3	89.7	0	0
Agrostophyllin	282.3	477.8	1	3	6.4	3.2	0	4	3	100	0	0
Coelogin	300.3	486.7	2	4	8	2.6	-0.4	7	3	100	0	1
Ferulic acid	194.2	420.2	2	4	8	1.4	-1.2	2	3	67.2	0	0
Coeloginanthridin	288.3	497.1	3	4	9.7	2.1	-0.9	7	3	87.7	0	1
Densiflorol B	254.2	465.3	1	6	9.8	1.2	-0.9	2	3	79.4	0	0
Sinapic acid	224.2	460.1	2	4	8.3	1.5	-1.3	3	3	68.2	0	0
Caffeic	180.2	392.5	3	4	9.9	0.6	-1.6	2	2	54.2	0	1
Cisferulic acid	194.2	405.5	2	4	7.8	1.4	-1	2	3	69.7	0	0
Gigantol	274.3	554.5	2	3	7.5	3.4	-0.9	6	3	100	0	0
Quercetin	302.2	512.2	4	5	14.4	0.4	-2.3	5	2	52.9	0	1
Apigenin	270.2	537.1	2	4	10.6	1.9	-1.7	3	3	75.3	0	0
Luteolin	286.2	503.7	3	5	12.3	1	-1.9	4	3	61.6	0	0
Kaempferol	286.2	501.4	3	5	12.3	1.1	-1.8	4	3	64.7	0	0
Myricetin	318.2	523.1	5	6	16.4	-0.3	-2.8	6	2	28	1	1
Denbinobine	284.3	496.7	1	6	10	1.4	-0.7	3	3	85.1	0	0
Batatasin 3	244.3	514.4	2	2	7.2	3	-0.8	5	3	100	0	0
Coelonin	242.3	477.9	2	2	7.4	2.6	-0.6	5	3	95.1	0	0
Flaccidinin	270.3	473.2	2	3	7.7	2.4	-0.5	6	3	95.7	0	0
Callosinin	298.3	501.4	0	3	4.1	3	-0.4	6	3	100	0	0
Imbricatin	270.3	463.6	2	3	7.8	2.4	-0.4	6	3	95.7	0	0
Coeloginin	314.3	495.4	1	5	7.7	2.1	-0.9	6	3	86.8	0	0
Isooxoflaccidin	284.3	472.1	2	5	9.9	1.5	-0.9	5	3	82	0	0
Tristin	260.3	529	3	3	9.4	2.3	-1.4	6	3	84.1	0	0
Phaitanthrin A	306.3	538.4	0	6	9	2.2	-0.7	2	3	90.7	0	0
6,methoxycoeloni n	272.3	505.6	2	3	7.6	2.7	-0.6	6	3	96	0	0
1,8 Cineole	332.4	563	4	11	17.2	0.2	-1.1	5	3	74.7	0	0
Callosin	272.3	517.4	2	3	7.6	2.8	-0.7	6	3	96.2	0	0
Aeridin	300.3	495.1	2	4	8.1	2.6	-0.5	7	3	100	0	1
Habenariol	358.4	647.2	3	4	10.3	3.8	-1.5	4	3	94.9	0	0
2,3 Tetramethoxyphe nanthrene	298.3	531.8	0	3	4.4	3.6	-0.5	4	3	100	0	0
Callosumidin	314.3	543.4	2	5	9.1	2.7	-0.6	5	3	100	0	0
Flavanthrin	482.5	761.9	4	5	13.4	4.8	-1.6	6	1	100	0	2

Table 3.2: Interaction of plant compounds with Hepcidin

NAME OF THE LIGAND	RESIDUES INTERACTION	BOND LENGTH (Å)	NO.OF BONDS FORMED	G.SCORE (Kcal/mol)
DENDROBIUM NOBILE				
Moscatilin (176096)	CYS 5(H-O)	2.0	4	-6.43
	LYS13(O-H)	2.2		
	MET16(H-O)	1.7		
	MET16(O-H)	2.3		
Gigantol(3085362)	LYS19(O-H)	2.5	4	-4.4
	LYS18(O-H)	2.1		
	MET16(H-O)	1.9		
	LYS13(H-O)	2.1		
Denbinobine(10423984)	LYS19(O-H)	2.0	3	-2.81
	ARG11(O-H)	1.9		
	MET16(H-O)	2.1		
1,8Cineole(73815050)	LYS19(O-H)	2.0	5	-5.74
	MET16(H-O)	2.1		
	LYS13(H-O)	1.9		
	ARG11(O-H)	2.5		
	ARG11(H-O)	1.8		
AERIDES ODORATUM				
Gallic acid(370)	LYS19(O-H)	2.5	4	-5.04
	LYS19(O-H)	1.8		
	LYS13(H-O)	2.1		
	LYS13(H-O)	1.8		
Syringic acid(10742)	LYS13(H-O)	1.9	4	-4.05
	LYS19(O-H)	2.3		
	LYS19(O-H)	2.3		
	LYS19(O-H)	1.8		
Catechin(73160)	MET16(H-O)	2.0	4	-4.58
	MET16(O-H)	2.5		
	LYS13(H-O)	1.8		
	LYS13(H-O)	2.2		
Caffeic(689043)	CYS18(O-H)	2.0	3	-4.59
	LYS13(H-O)	1.8		
	LYS13(H-O)	1.8		
Sinapic acid(637775)	ARG11(O-H)	1.7	3	-3.89
	ARG11(O-H)	2.1		
	MET16(H-O)	1.9		
Quercetin(5280343)	LYS13(H-O)	1.9	2	-4.29
	LYS13(H-O)	1.9		
Apigenin(5280443)	GLY15(H-O)	2.2	4	-4.52
	LYS13(H-O)	2.0		
	MET16(H-O)	2.1		
	LYS19(O-H)	1.8		
Kaempferol(5280863)	MET16(H-O)	2.1	4	-3.08
	CYS5(H-O)	2.2		
	GLY15(H-O)	2.4		
	LYS19(O-H)	1.8		
Myricetin(5281672)	HIS10(N-H)	2.3	4	-4.87

	LYS13(H-O)	1.9		
	LYS13(H-O)	1.9		
	ARG11(O-H)	2.1		
Ferulic acid (445858)	LYS13(H-O)	2.1	3	3.91
	LYS19(O-H)	1.9		
	LYS13(H-O)	2.0		
GASTRODIA ELATA				
Vanillin(1183)	LYS19(O-H)	1.8	3	-3.16
	GLY15(O-H)	2.4		
	LYS13(H-O)	1.9		
Vanillyl alcohol(62348)	MET16(H-O)	1.9	3	-3.41
	LYS13(H-O)	2.2		
	GLY15(O-H)	2.6		
Gastrodin(115067)	MET16(O-H)	2.4	5	-4.67
	HIS10(H-N)	2.3		
	HIS10(O-H)	2.5		
	ARG11(H-O)	2.0		
	LYS13(H-O)	2.0		
CEPHALANTHEROPSIS GRACILIS				
Isatin(7054)	LYS19(O-H)	1.9	2	-3.19
	MET19(H-O)	1.9		
Indole 3 carboxylic acid(73530)	CYS18(O-H)	2.3	1	-1.88
Cisferulic acid(1548883)	LYS13(H-O)	1.8	4	-4.36
	GLY15(O-H)	2.4		
	LYS19(O-H)	1.9		
	LYS19(O-H)	1.9		
Phaitanthrin A(24970702)	LYS19(O-H)	2.2	3	-3.81
	MET16(O-H)	1.7		
	LYS19(O-H)	2.1		
Flavanthrin(102004681)	LYS19(O-H)	1.9	2	-2.37
	LYS13(O-H)	1.9		
ARUNDINA GRAMNIFOLIA				
Vanillic acid(8468)	LYS19(O-H)	2.5	4	-4.79
	LYS19(O-H)	1.8		
	GLY15(O-H)	2.0		
	LYS13(H-O)	1.8		
Syringaldehyde(8655)	LYS13(H-O)	2.0	1	-3.34
Densiflorol B (637413)	LYS13(H-O)	2.0	2	-2.98
	ARG11(H-O)	2.4		
Batatasin 3(10466989)	LYS13(H-O)	2.2	4	-3.59
	LYS19(O-H)	2.5		
	MET16(H-O)	1.9		
	LYS19(O-H)	2.1		
Coelonin(11390848)	LYS19(O-H)	1.7	2	-2.99
	LYS13(O-H)	1.9		
Aristin(15736297)	LYS13(H-O)	2.3	2	-2.58
	MET16(H-O)	1.9		
EULOPHIA NUDA				
Nudol(158975)	LYS19(O-H)	1.9	2	-3.28
	LYS13(H-O)	2.0		
AGROSTOPHYLLUM CALLOSUM				
Orchinol(181686)	LYS19(O-H)	2.0	2	-3.03
	LYS13(H-O)	2.0		
Flaccidinin(14235431)	GLY15(O-H)	2.2	2	-3.44

	LYS13(H-O)	1.5		
6-Methoxycoelonin (45267920)	HIS10(O-H)	2.5	2	-3.06
	ARG11(H-O)	1.8		
Callosuminin(101995283)	LYS19(O-H)	2.0	2	-2.9
	LYS19(O-H)	2.4		
Callosinin(14235433)				-2.62
Imbricatin(14237636)	GLY15(O-H)	2.1	2	-2.84
	LYS13(H-O)	2.1		
Callosumidin(101995816)	LYS13(H-O)	1.7	1	-1.37
Isoflaccidin(14890492)	GLY7(O-H)	1.9	2	-2.77
	GLY15(O-H)	2.0		
Callosin(86182261)	ARG11(O-H)	2.5	3	-3.05
	ARG11(H-O)	1.9		
	MET16(H-O)	2.3		
BULBOPHYLLUM ODORATISSIMUM				
Bulbophyllanthrone(398641)	LYS19(O-H)	2.4	2	-2.74
	LYS13(H-O)	2.0		
COELOGYNE CRISTATA				
Coelogin(442697)	LYS13(H-O)	2.1	2	-2.98
	LYS19(O-H)	2.3		
Coeloginanthridin(636881)	LYS13(H-O)	2.1	2	-3.47
	MET16(H-O)	2.0		
Coeloginin(14427337)	ARG11(H-O)	-2.4	1	-2.48
AERIDES CRISPUM				
Aeridin(86201516)	LYS19(O-H)	1.9	3	-3.36
	LYS19(O-H)	2.3		
	LYS13(H-O)	1.9		
HABENARIA REPENS				
Habenariol(100989770)	TYS13(H-O)	1.9	4	-4.36
	TYS19(O-H)	2.5		
	MET16(O-H)	1.7		
	CYS18(O-H)	2.0		

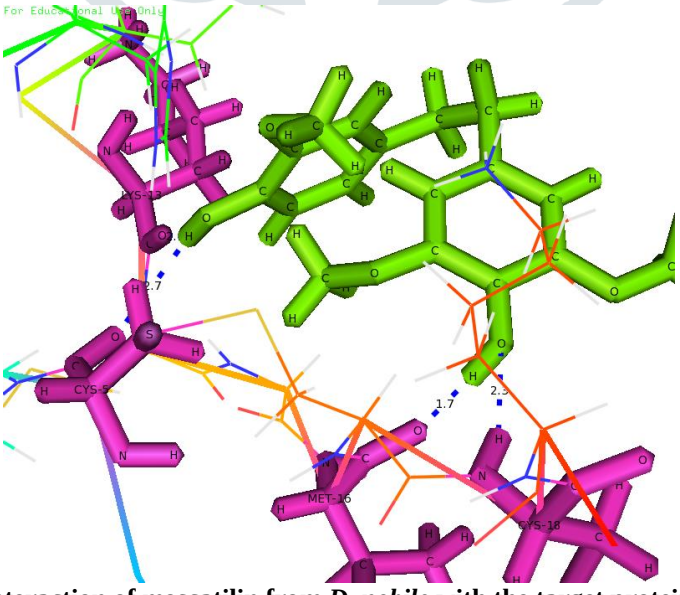

Fig. 3.1: Interaction of moscatilin from *D. nobile* with the target protein hepcidin

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