Pharmacokinetic Attributes for Natural and Chemical Anti-Anemic Agents with Promising Specific Proteins by Docking Analysis

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ABSTRACT

Anemia, being one of the most significant genetic haematological disorders afflicting people of Indian descent, has been managed with it as well as a plethora of other pathological conditions. Throughout this investigation, potential target proteins for drugs and bio-actives are identified and evaluated. Analyses of bioactive agent's *in silico* anti-sickling activity were conducted. Chlorogenic acid and catechin, the bio-actives found in wheat grass and the betel plant, are being studied against two anemia related target receptors: Hepcidin and transferrin. The assessment was made using the binding-free energy value as well as the different interactions between the amino acids at the receptors and the ligand. Detailed evaluation of the ligands' binding positions revealed the appearance of desirable interactions, such as hydrogen bonds, π-cation, Van der waals, and hydrophobic bonds. The results strengthen the body of research supporting the use of natural bio-actives in the treatment of anemia.

Keywords: Molecular docking; Hepcidin; Transferrin; Anemia; Chlorogenic acid; Catechin

INTRODUCTION

One quarter of the global population suffers from anemia, a health issue [1]. It affects people of all ages and even from almost every country, nonetheless, it affects children and pregnant women more frequently [2]. As in the majority of third world nations, anemia has reached epidemic proportions [3]. According to statistics, the most common micronutrient insufficiency, iron deficiency, is just to account for 50% of anemia cases. According to the WHO, hemoglobin levels below 12 gram percent for women and below 13 gram percent for men are considered to be anemic [4,5]. Four subunits make up the globular protein known as Hemoglobin (Hb). Two of these subunits stand in for chains, while the other two stand out for chains [6]. A heme group with an iron atom in the middle makes up each subunit. The deoxyhemoglobin molecule (deoxyHb) is a form of Hb that contains no other additional molecules. Patients with iron deficiency anemia have high serum levels of the hepatic hormone hepcidin, which regulates iron metabolism (IDA) [7]. Numerous studies have shown that some anemic people may not benefit from taking oral iron supplements. These individuals' have high blood hepcidin levels which increase the restriction of iron absorption, leading to a persistent

iron deficiency. To treat this condition, different methods are designed to block the formation of hepcidin. While antigen therapy aims to reduce hepcidin mRNA, the most frequently used treatments affect hepcidin synthesis through iron signaling, inflammatory, and erythropoiesis pathways.

The blood plasma protein known as human Transferrin (hTf) is widely known for its function in the transport of iron. This protein may be able to carry additional metal ions or organometallic compounds from the bloodstream to all cell tissues, even if it only has 30% of its Fe^{+3} binding capacity. A crucial part in preserving iron homeostasis is played by the therapeutically relevant protein known as human Transferrin (hTf) [8]. Studies on hTf are important because iron accumulation in the CNS plays a crucial role in neurodegenerative diseases. HTF is a glycoprotein, with a molecular mass of 79.6 kDa and 679 amino acid residues. Since they contain therapeutic capabilities, medicinal plants, known for their illustrious history, have been frequently used as medical treatments. Various investigations and clinical trials have tested with these substances' primary ingredients, which serve as replacements for various medicinal goals [9-11]. The creation of numerous drugs that have been used successfully for numerous

disorders was made possible by medicinal plants. *Triticum aestivum* L., also referred as wheat grass, is a member of the poaceae or gramineae family of monocotyledonous flowering plants, generally called as grasses. *Piper betle* L., also called as betel vine, is a member of the genus piper of the family piperaceae. Phenomenal health benefits of *Triticum aestivum* and *piper betel* for its antioxidant and anti-anemic activity have been systematically reported by Johri et al., presenting that the plants' extract aids to assist its antioxidant properties. The numerous bio active compounds found in betel leaf and fruit indicate their ability to be utilized in a variety of medicinal processes [12]. To maintain good health, wheatgrass is ingested in India as a pill or juice. Wheat grass juice is well known for having therapeutic capabilities that can treat a variety of degenerative disorders. It is also highly helpful in treating thalassemia, ulcerative colitis, anemia, and other conditions that benefit various body regions. In this study, the molecular docking technique, which is quickly emerging as a key tool in pharmaceutical research, was used to predict the binding affinities of several synthetic and herbal components for active regions of hepcidin and transferrin [13-15]. Molecular docking is gaining importance in structure-based molecular genetics and computer aided drug development. By leveraging molecular docking technology to demonstrate how a little ligand and a protein interact at the nano scale, microscopic particles may be used to describe how significant biochemical processes take place and behave at the protein binding site. By applying various computational techniques and *in-silico* analyses, this work can be analyzed. Understanding how metabolites enter a receptor's binding site and figuring out the compound's binding affinity are both necessary for docking and identifying the druggable target. Genome annotation, proteomics experiment design, and the identification of new targets for vaccines, drugs, and diagnostics are also essential the entire proteome's Protein-Protein Interactions (PPI) or identifying the specific host-pathogen connection between a collection of proteins can be helpful in developing prospective therapeutic targets [16].

MATERIALS AND METHODS

Data tracking

3 dimensional structural composition of potential protein targets both hepcidin, transferrin from the protein data bank were downloaded with their respective PDB ID's in a folder. A total of two proteins were retrieved. CASTp[11] was used to anticipate the proteins' active sites. Computed atlas of surface topography of proteins. Recent theoretical and algorithmic developments in computational geometry are the foundation of CASTp. It offers a lot of benefits:

- Analytical identification of pockets and cavities.
- Accurate definition of the border between the bulk solvent and the pocket.
- Rotational invariance of all derived parameters, absence of discretization, dot surface, or grid points.

The 2 dimensional structure of catechin, chlorogenic, 3, 4-dihydroxybenzaldehyde, folic acid, dasatinib, $Fe^{(3+)}$-ascorbate, gluconate were retrieved from PubChem with their respective PubChem CID in a separate ligand folder.

Molecular docking studies

For understanding the proteins and ligands interactions, molecular docking analysis was practiced using the software's PyRx-python prescription 0.8 in windows 10 home single language. Preparation of the protein-ligand interaction was made using auto dock tools-1.5.7 software. In the simulated space, the generation of the proteins hepcidin (1m4f) and transferrin (3qyt) includes adding polar hydrogens with unified atom kollman charges. Ligands (catechin, chlorogenic acid, 3, 4-dihydroxybenzaldehyde, folic acid, dasatinib, $Fe^{(3+)}$-ascorbate, ferric gluconate) were prepared by adding polar hydrogens, along a gasteiger charge, with the detection of flexible torsions, and a setting for the number of torsions were added to prepare them. Based on the dimensions of each protein's active site, gridbox were described. Are used as the exhaustiveness factor to provide more consistent docking results. The optimum position with low affinity was chosen after manual interaction analysis and the maintenance of many conformations. Protein-ligand docking studies were done using the crystal structures of approved protein therapeutic targets.

The bio active compounds and synthetic drugs utilizing the Swiss-ADME software were simulated screened. To evaluate the molecules using the Lipinski rule and criteria for drug-likeness, such as pharmacokinetic parameters clearly shown in the Table 1 along with Table 2.

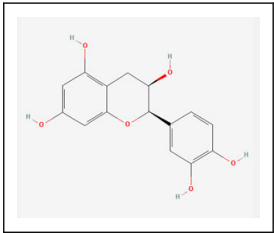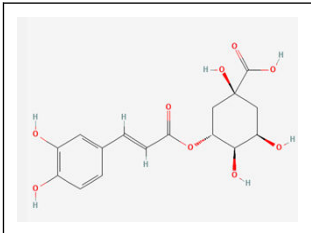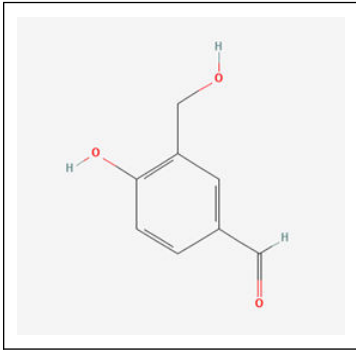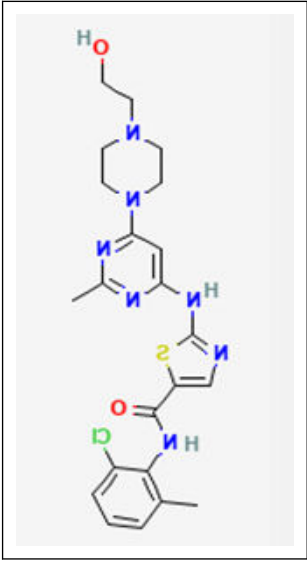**Table 1:** Predicted physicochemical properties of natural ligands.
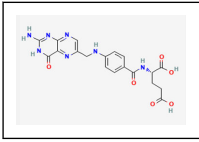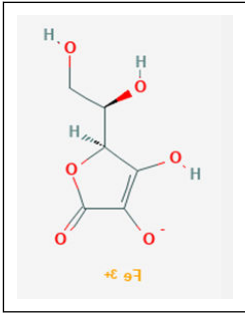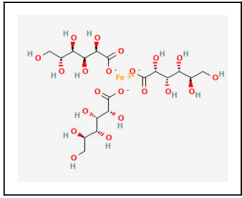
Physicochemical properties	Catechin	Chlorogenic acid	3,4-Dihydroxybenzaldehyde
Chemical structure			
Formula	$C_{15}H_{14}O_6$	$C_{16}H_{18}O_9$	$C_7H_5NO_5$
Molecular weight	290.27 g/mol	354.31 g/mol	183.12 g/mol
Num heavy atoms	21	25	13
Num arom heavy atoms	12	6	6
Fraction Csp3	0.2	0.38	0
Num. rotatable bonds	1	5	2
Num. H-bond acceptors	6	9	5
Num. H-bond donors	5	6	2
Molar refractivity	74.33	83.5	44.7
Topological polar Surface area	110.38 Å²	164.75 Å²	103.35 Å²
GI absorption	High	Low	Low
BBB permeant	No	No	No
P-gp substrate	Yes	No	No
CYP1A2 inhibitor	No	No	No
CYP2C19 inhibitor	No	No	No
CYP2C9 inhibitor	No	No	No
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	No	No	No
Log Kp (skin permeation)	-7.82 cm/s	-8.76 cm/s	-8.76 cm/s

Table 2: Predicted physicochemical properties of synthetic ligands.

Physico chemical properties	Dasatinib	Folic acid	Ferric-ascorbate	Ferric gluconate
Chemical structure				
Formula	$C_{22}H_{26}ClN_7O_2S$	$C_{19}H_{19}N_7O_6$	$C_6H_7FeO_6^{++}$	$C_{18}H_{33}FeO_{21}$
Molecular weight	488.01 g/mol	441.40 g/mol	230.96 g/mol	641.29 g/mol
Num. heavy atoms	33	32	13	40
Num. arom. heavy atoms	17	16	0	0
Fraction Csp3	0.36	0.21	0.5	0.83
Num. rotatable bonds	8	10	2	15
Num. H-bond acceptors	6	9	6	21
Num. H-bond donors	3	6	3	15
Molar refractivity	138.63	111.92	33.18	109.78
Topological polar surface area	134.75 Å²	213.28 Å²	110.05 Å²	423.84 Å²
GI absorption	High	Low	High	Low
BBB permeant	No	No	No	No
P-gp substrate	No	No	Yes	Yes
CYP1A2 inhibitor	No	No	No	No
CYP2C19 inhibitor	Yes	No	No	No
CYP2C9 inhibitor	Yes	No	No	No
CYP2D6 inhibitor	Yes	No	No	No
CYP3A4 inhibitor	Yes	No	No	No

Log Kp (skin permeation)	-6.73 cm/s	-9.76 cm/s	-8.87 cm/s	-17.38 cm/s

The investigated compounds are then subjected to molecular docking using auto dock tools (version 1.5.7) and PyRx-Python prescription 0.8 in a Windows 10 home single language workstation to properly evaluate their ability to bind to the iron-binding receptor, transferrin (3qyt), and iron ion transmembrane transporter inhibitor; signaling receptor, hepcidin (1m4f).

RESULTS

Data collection

In this paper, 2D structures of (catechin, chlorogenic acid, 3,4-dihydroxybenzaldehyde, folic acid, dasatinib, ferric gluconate, and 3+-ascorbate] were obtained from PubChem and drug bank sites. Two proteins in total-hepcidin (1m4f) and transferrin (3qyt) were downloaded from the protein data bank website.

Molecular docking

The binding energy of the compounds (catechin, chlorogenic acid, 3,4-dihydroxybenzaldehyde, folic acid, dasatinib, $Fe^{(3+)}$-ascorbate, ferric gluconate) to the active site of target proteins was used to determine their affinity displayed in Table 3. So, using PyRx and AutoDockTools, seven ligands were docked to two proteins. The distribution of protein targets with high ligand binding affinity. The top seven ligands with high affinity. Further study was carried out on proteins with binding energies between 11 kcal/mol and 7 kcal/mol, and these proteins were considered as potential targets for protein-ligand interaction analyses.

Table 3: List of highly interacting ligands and their binding energies against hepcidin and transferrin where RMSD stands for Root-Mean-Square Deviation to calculate the rank as only moveable heavy atoms are used to compute RMSD values, which are generated in relation to the best mode (the first model) (*i.e.* only ligand atoms, not hydrogen). Each atom in one conformation is matched with itself in the opposite conformation by RMSD upper limit, which excludes any symmetry. Each atom in one conformation is paired with the nearest atom of the same element type in the opposite conformation using the RMSD lower bound.

S. no.	Ligands	Binding affinity (kcal/mol)	RMSD/ub	RMSD/lb
1.	Transferrin and dasatinib	-9	8.733	4.224
2.	Transferrin and follic acid	-8.1	2.213	1.691
3.	Transferrin and catechin	-7.2	3.003	1.818
4.	Transferrin and cholorogenic acid	-7	19.654	17.838
5.	Hepcidin and folic acid	-6.6	5.963	3.33
6.	Hepcidin and dasatinib	-5.8	20.904	20.418
7.	Transferrin and ferric ascorbate	-5.6	2.62	1.746
8.	Transferrin and benzaldehyde bihydroxy	-5.5	16.233	15.288
9.	Transferrin and ferric gluconate	-5.4	15.644	14.477
10.	Hepcidin and catechin	-4.9	7.085	2.973
11.	Hepcidin and cholorogenic acid	-4.8	6.59	1.786
12.	Hepcidin and ferric ascorbate	-4.4	2.802	2.428

| 13. | Hepcidin and ferric gluconate | -3.9 | 2.742 | 1.709 |
| 14. | Hepcidin and benzaldehyde bihydroxy | -3.5 | 3.336 | 1.741 |

Receptors-ligands interaction study

The protein data bank accession numbers 1m4f and 3qyt, transferrin, an iron receptor, and hepcidin, an iron ion transmembrane transporter inhibitor; signal receptor.

Following compound identification, only 7 compounds were chosen for molecular docking based on the virtual screening and their pharmacokinetic and pharmacodynamic characteristics. The targets were determined to be transferrin and hepcidin. When compared to the control medication, the two compounds with the highest binding affinities are catechin and chlorogenic

acid with transferrin. Catechin showed serine and histidine with two different hydrogen bonds interacting with transferrin protein (Table 4). Chlorogenic acid demonstrated hydrogen bonds with two different amino acids: Two with arginine alone, one with glutamine, and two with methionine. In contrast, the control drug dasatinib demonstrated four hydrogen bonds with various amino acids: Tyrosine, lysine, glutamine, and methionine of the transferrin receptor displayed in Figures 1-13.
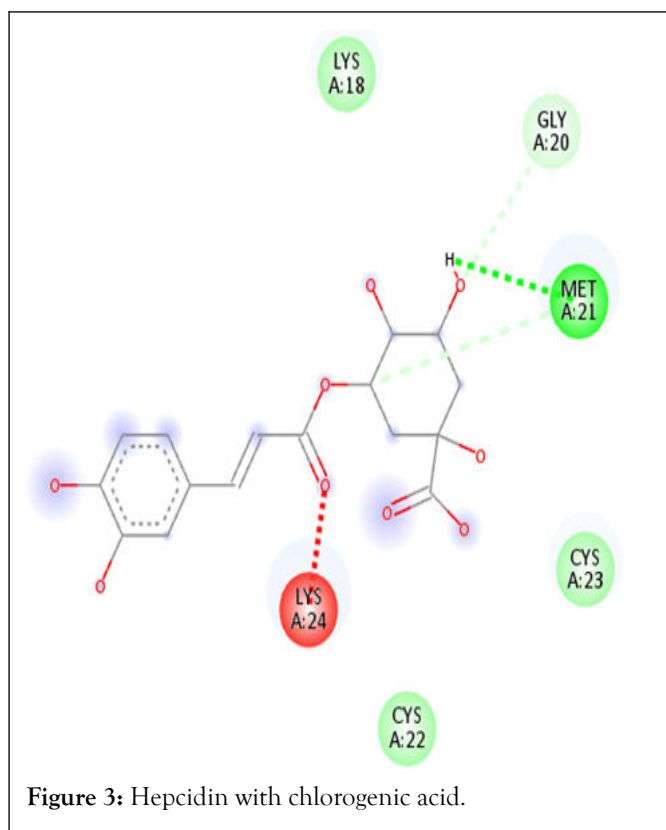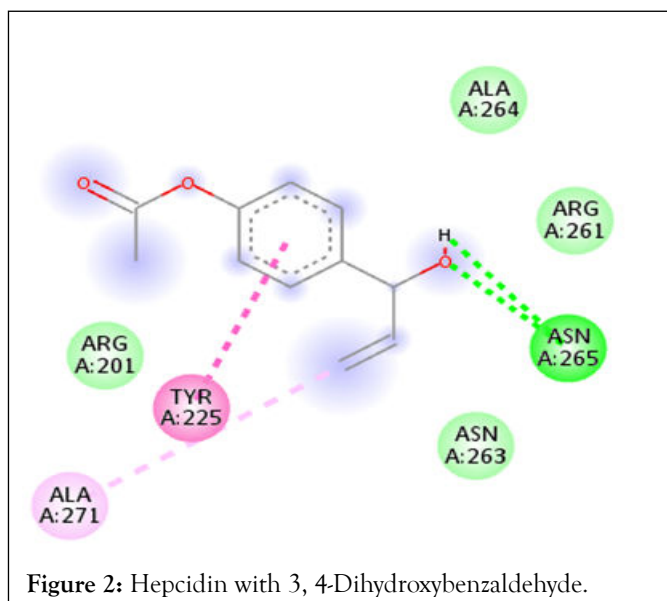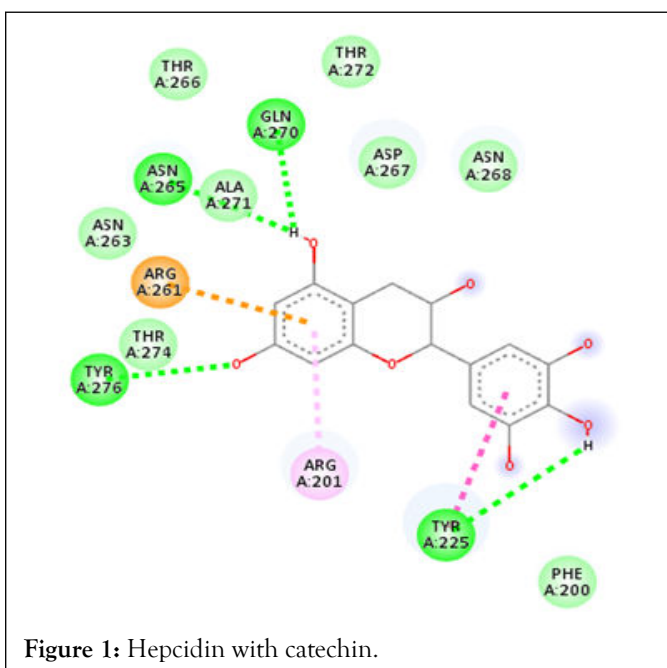
Table 4: Predicted functional partners of hepcidin.

Proteins	Functions
SLC40A1	Solute carrier family 40 member 1; may be involved in iron export from duodenal epithelial cell and also in transfer of iron between maternal and fetal circulation. Mediates iron efflux in the presence of a ferroxidase (hephaestin and/or ceruloplasmin); belongs to the Ferro Portin (FP) (TC 2.A.100) family.
A2M	Alpha-2-macroglobulin; Is able to inhibit all four classes of proteinases by a unique 'trapping' mechanism. This protein has a peptide stretch, called the 'bait region' which contains specific cleavage sites for different proteinases.
HFE2	Hemojuvelin; acts as a Bone Morphogenetic Protein (BMP) coreceptor. Through enhancement of BMP signaling regulates hepcidin (HAMP) expression and regulates iron homeostasis; belongs to the Repulsive Guidance Molecule (RGM) family.
HFE	Hereditary hemochromatosis protein; binds to Transferrin Receptor (TFR) and reduces its affinity for iron loaded transferrin; belongs to the MHC class I family.
TFR2	Transferrin receptor protein 2; mediates cellular uptake of transferrin bound iron in a non-iron dependent manner. May be involved in iron metabolism, hepatocyte function and erythrocyte differentiation; belongs to the peptidase M28 family.
FAM132B	Erythroferrone; iron-regulatory hormone that acts as an erythroid regulator after hemorrhage: Produced by erythroblasts following blood loss and mediates suppression of hepcidin (HAMP) expression in the liver, thereby promoting increased iron absorption and mobilization from stores. Promotes lipid uptake into adipocytes and hepatocytes *via* transcriptional up-regulation of genes involved in fatty acid uptake.
SLC11A2	Natural resistance associated macrophage protein 2; important in metal transport, in particular iron. Can also transport manganese, cobalt, cadmium, nickel, vanadium and lead. Involved in apical iron uptake into duodenal enterocytes. Involved in iron transport from acidified endosomes into the cytoplasm of erythroid precursor cells. May play an important role in hepatic iron accumulation and tissue iron distribution. May serve to import iron into the mitochondria.

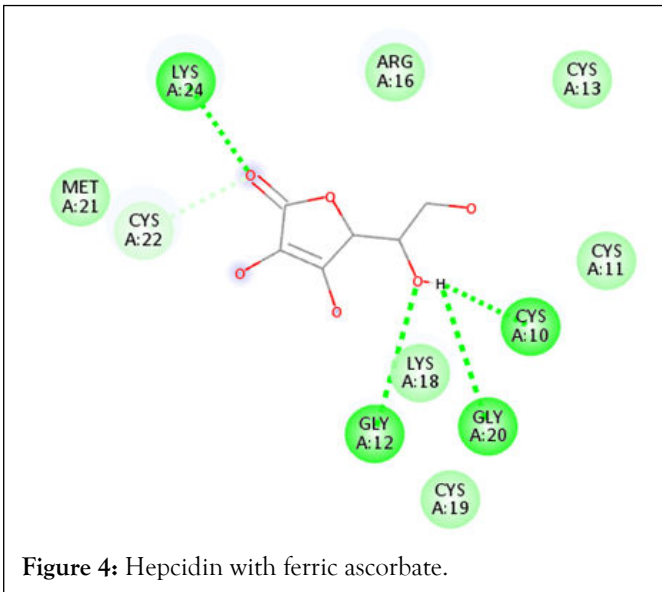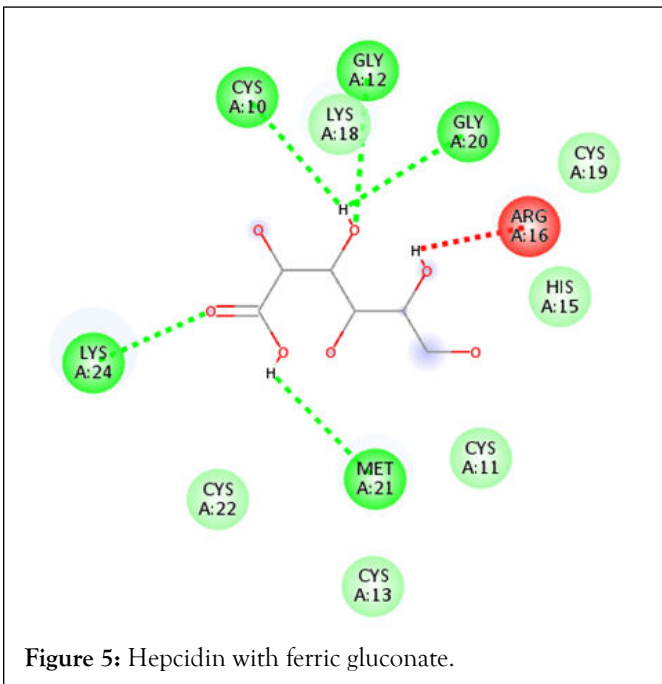| TMPRSS6 | Transmembrane protease serine 6; serine protease which hydrolyzes a range of proteins including type I collagen, fibronectin and fibrinogen. Can also activate urokinase-type plasminogen activator with low efficiency. May play a specialized role in matrix remodeling processes in liver. Through the cleavage of HFE2, a regulator of the expression of the iron absorption regulating hormone hepicidin/HAMP, plays a role in iron homeostasis. |
| TFRC | Transferrin receptor protein 1; cellular uptake of iron occurs *via* receptor mediated endocytosis of ligand-occupied transferrin receptor into specialized endosomes. Endosomal acidification leads to iron release. The apotransferrin-receptor complex is then recycled to the cell surface with a return to neutral pH and the concomitant loss of affinity of apotransferrin for its receptor. Transferrin receptor is necessary for development of erythrocytes and the nervous system (by similarity). |

Figure 1: Hepcidin with catechin.

Figure 3: Hepcidin with chlorogenic acid.

Figure 2: Hepcidin with 3, 4-Dihydroxybenzaldehyde.

Figure 4: Hepcidin with ferric ascorbate.

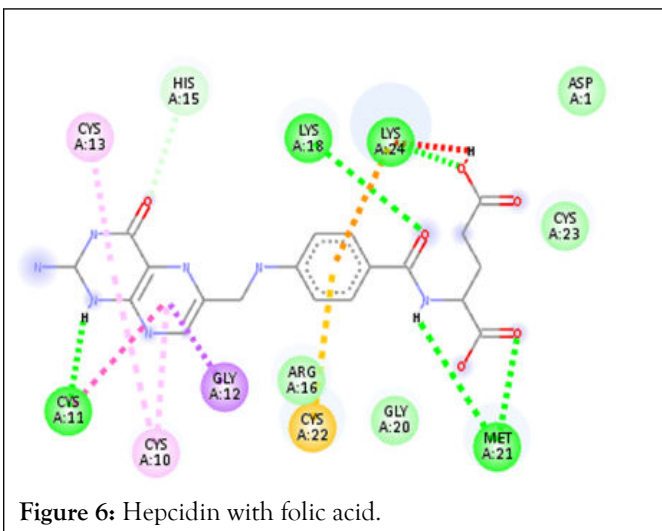**Figure 5:** Hepcidin with ferric gluconate.
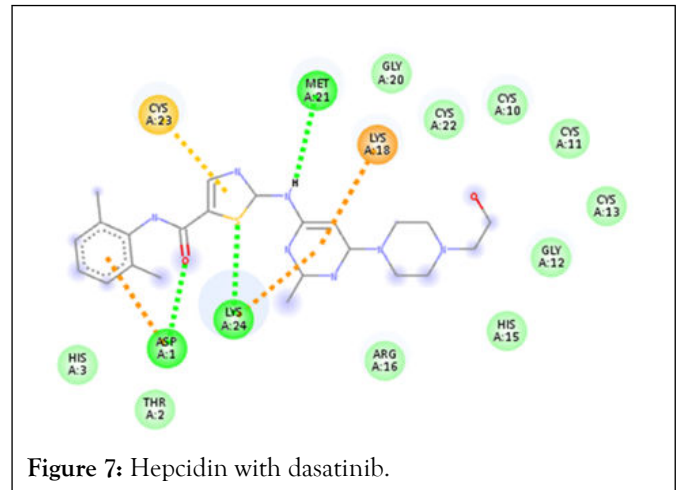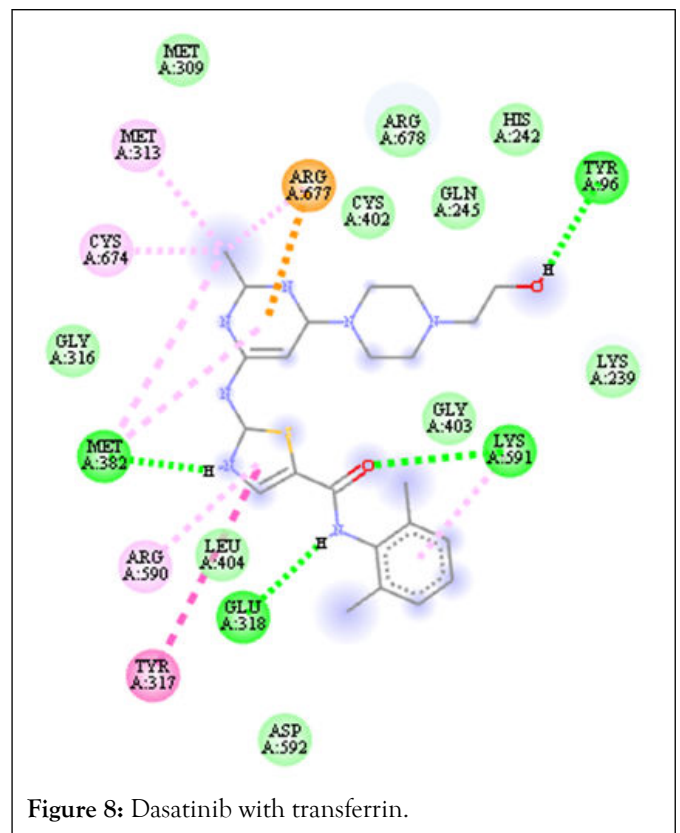

Figure 6: Hepcidin with folic acid.

Figure 7: Hepcidin with dasatinib.

Figure 8: Dasatinib with transferrin.
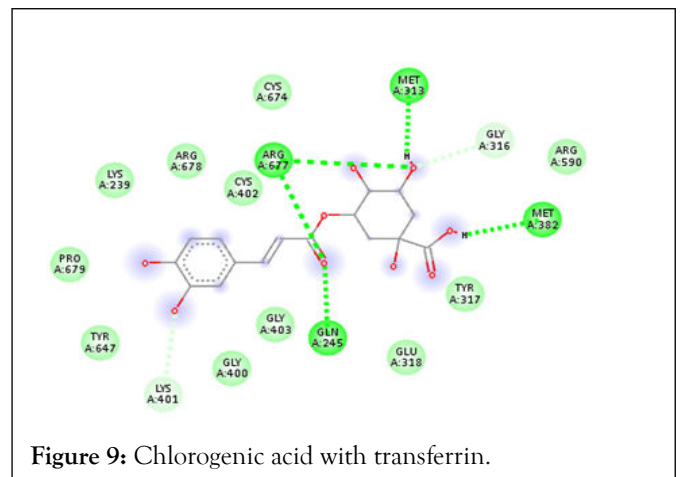
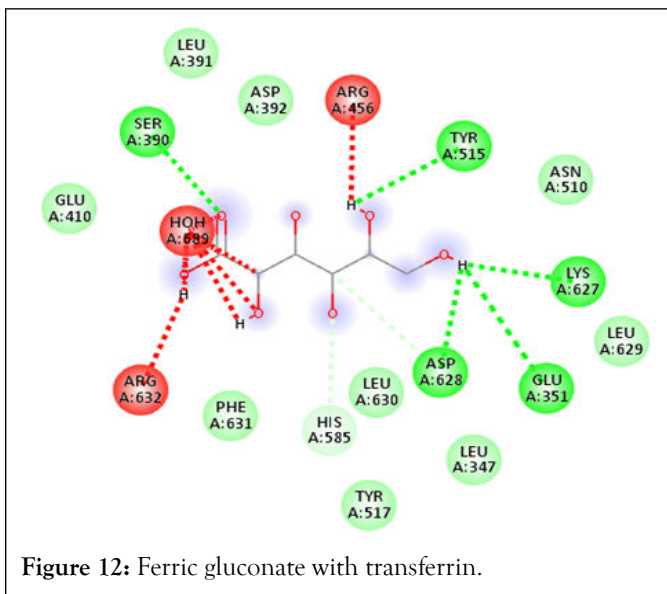**Figure 9:** Chlorogenic acid with transferrin.

Figure 10: Catechin with transferrin.

Figure 11: Ferric ascorbate with transferrin.

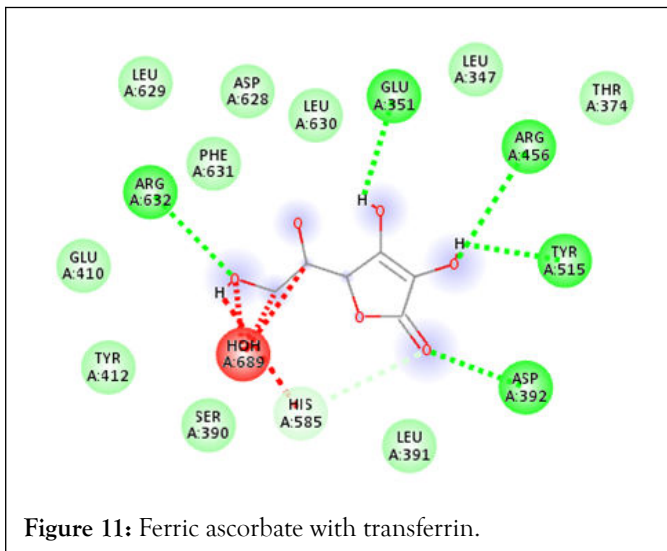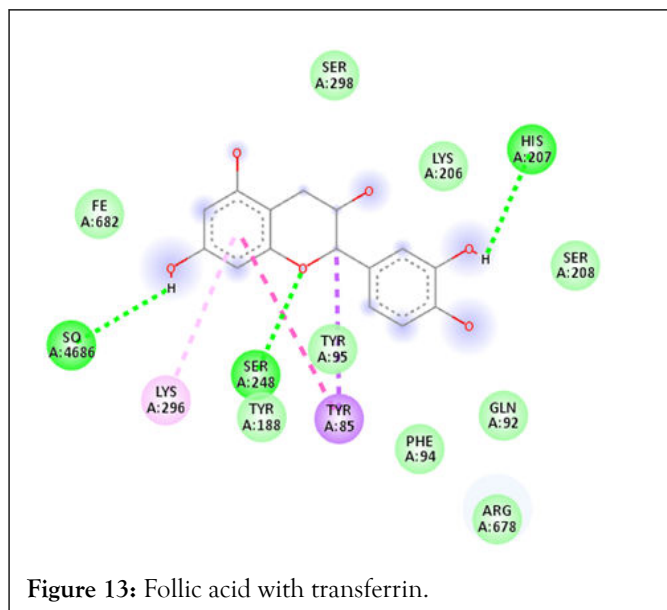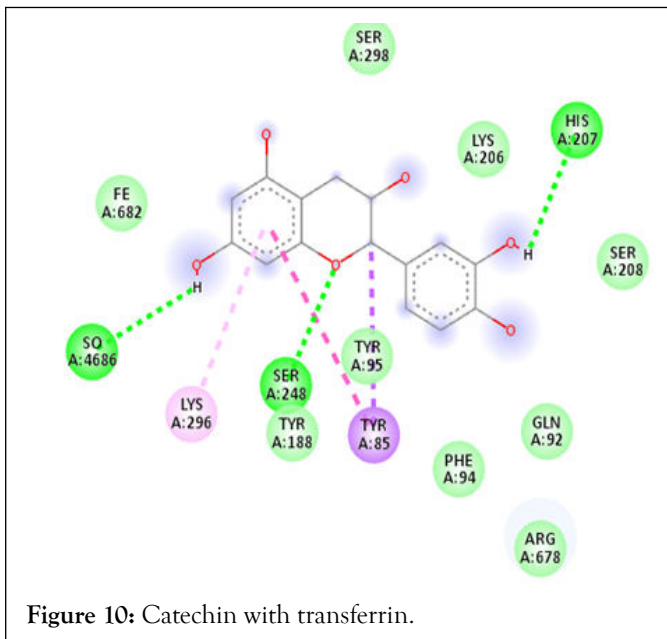**Figure 12:** Ferric gluconate with transferrin.

Figure 13: Follic acid with transferrin.

DISCUSSION

The physiological functions of the human body, including the delivery of oxygen to tissues and the storage and use of energy, depend heavily on iron. The proteins are divided into three categories based on their ligand affinities. The value of binding affinity, which ranges from 12 kcal/mol to 8 kcal/mol a as high affinity, defined. Low affinity is defined as binding affinity values less than 5 kcal/mol and moderate affinity as binding affinity values between 7.9 kcal/mol and 5 kcal/mol. New drug candidates are typically found using the Lipinski criteria, which include molecular weight, the number of H-bond donors present, the number of H-bond acceptors present, and the octanol-water partition coefficient (LogP). A molecular weight of less than 500 Da is advised. Smaller molecules require less energy to link together and form more durable bonds. A drug's capacity to pass a cell membrane is assessed using an H-bond donor and acceptor. The cell's permeability diminishes as the number of H-bonds rises. A compound's ability to dissolve in fat is determined by its logP or lipophilicity. Lower toxicity results from a compound's increased hydrophilicity when its lipophilicity declines [17]. Catechin and chlorogenic acid have demonstrated good binding affinity with the transferrin receptor in the current investigation, indicating a beneficial effect on the improvement of iron absorption. These bioactive agents can be found in the wheat grass and betel plant. It has been used to treat hyperglycemia, acute microbiological infection, a skin condition, inflammation, anemia, and local anesthetics (Tables 5-7) [18,19].

Table 5: Disease-gene associations of Hepcidin.

Diseases	Matching proteins in the network of Hepcidin
Hemochromatosis	SLC40A1, HFE2, TFRC, TMPRSS6, SLC11A2, HFE, TFR2, HAMP
Hemochromatosis type 4	SLC40A1, HFE2, HFE, TFR2, HAMP
Iron deficiency anemia	HFE2, TFRC, TMPRSS6, SLC11A2, HAMP
Acquired metabolic disease	A2M, HFE2, TFRC, TMPRSS6, SLC11A2, HFE, TFR2, HAMP
Hemochromatosis type 2	HFE2, HFE,TFR2, HAMP
Disease of metabolism	SLC40A1, A2M, HFE2, TFRC, TMPRSS6, SLC11A2, HFE, TFR2, HAMP
Hemochromatosis type 1	HFE2, HFE, TFR2
Hemochromatosis type 3	HFE2, HFE, TFR2
Microcytic anemia	TMPRSS6, SLC11A2, HAMP
Anemia	EPO, TMPRSS6, SLC11A2, HFE, HAMP
Iron metabolism disease	HFE, TFR2, HAMP
Hypochromic microcytic anemia	TMPRSS6, HAMP
Atransferrinemia	HFE2, TFR2
African iron overload	SLC40A1, HFE
Siderosis	HFE, HAMP
Hemosiderosis	HFE, HAMP

Table 6: Predicted functional partners of transferrin.

Proteins	Functions
TFRC	Transferrin receptor protein 1; cellular uptake of iron occurs *via* receptor mediated endocytosis of ligand occupied transferrin receptor into specialized endosomes. Endosomal acidification leads to iron release. The apotransferrin-receptor complex is then recycled to the cell surface with a return to neutral pH and the concomitant loss of affinity of apotransferrin for its receptor. Transferrin receptor is necessary for development of erythrocytes and the nervous system (by similarity).
APOA1	Apolipoprotein A-I; participates in the reverse transport of cholesterol from tissues to the liver for excretion by promoting cholesterol efflux from tissues and by acting as a cofactor for the Lecithin Cholesterol Acyltransferase (LCAT).
SCG3	Secretogranin iii; member of the granin protein family that regulates the biogenesis of secretory granules. Acts as a sorting receptor for intragranular proteins including chromogranin A/CHGA (By similarity). May also play a role in angiogenesis.
SYNJ1	Synaptojanin-1; phosphatase that acts on various phosphoinositides, including phosphatidylinositol 4-phosphate, phosphatidylinositol (4,5)-bisphosphate and phosphatidylinositol (3,4,5)-risphosphate.

TFR2	Transferrin receptor protein 2; mediates cellular uptake of transferrin bound iron in a non-iron dependent manner. May be involved in iron metabolism, hepatocyte function and erythrocyte differentiation; belongs to the peptidase M28 family. M28B subfamily.
AHSG	Alpha-2-HS-glycoprotein; promotes endocytosis, possesses opsonic properties and influences the mineral phase of bone.
AMBP	Alpha-1-microglobulin/bikunin precursor; protein AMBP; Inter-alpha-trypsin inhibitor inhibits trypsin, plasmin, and lysosomal granulocytic elastase. Inhibits calcium oxalate crystallization; lipocalins.
ALB	Serum albumin; serum albumin, the main protein of plasma, has a good binding capacity for water, $Ca^{(2+)}$, $Na^{(+)}$, $K^{(+)}$, fatty acids, hormones, bilirubin and drugs. Its main function is the regulation of the colloidal osmotic pressure of blood. Major zinc transporter in plasma, typically binds about 80% of all plasma zinc; belongs to the ALB/AFP/VDB family.
APOA2	Apolipoprotein A-II; may stabilize HDL (High Density Lipoprotein) structure by its association with lipids, and affect the HDL metabolism; apolipoproteins.
HP	Haptoglobin-related protein; haptoglobin; As a result of hemolysis, hemoglobin is found to accumulate in the kidney and is secreted in the urine. Haptoglobin captures, and combines with free plasma hemoglobin to allow hepatic recycling of heme iron and to prevent kidney damage. Haptoglobin also acts as an antimicrobial; antioxidant has antibacterial activity and plays a role in modulating many aspects of the acute phase response.

Table 7: Disease-gene associations of transferrin.

Diseases	Matching proteins in transferrin network
Disease of metabolism	APOC3, APOB, APOA1, LCAT, ALB, HP, TFRC, APOA2, ABCA1, AHSG, HFE, TFR2, B2M
Acquired metabolic disease	APOC3, APOA1, ALB, TFRC, APOA2, AHSG, HFE, TFR2, B2M
Familial visceral amyloidosis	APOC3, APOA1, ALB, APOA2, B2M
Hypolipoproteinemia	APOB, APOA1, LCAT, ABCA1
Lipid metabolism disorder	APOC3, APOB, APOA1, LCAT, ABCA1
Inherited metabolic disorder	APOC3, APOB, APOA1, LCAT, HP, TFRC, ABCA1, HFE, TFR2
Tangier disease	APOA1, LCAT, ABCA1
Artery disease	FCGRT, APOB, APOA1, ALB, ABCA1
Hemochromatosis	TFRC, HFE, TFR2
Atherosclerosis	APOB, APOA1, ABCA1
Norum disease	APOA1, LCAT
Mineral metabolism disease	AHSG, HFE, TFR2

Hemochromatosis type 1	HFE, TFR2
Hemochromatosis type 3	HFE, TFR2
Familial combined hyperlipidemia	APOB, APOA1
Hemochromatosis type 4	HFE, TFR2
Viral hepatitis	ALB, AHSG
Hemochromatosis type 2	HFE, TFR2
Iron metabolism disease	HFE, TFR2
Disease	FCGRT, APOC3, APOB, APOA1, LCAT, ALB, HP, TFRC, APOA2, ABCA1, AHSG, SYNJ1, HFE, TFR2, B2M
Proteinuria	ALB, HP

CONCLUSION

These two plants, *Piper betel* Linn and *Triticum aestivum* Linn, were chosen because of their greater and more suggestive iron concentration. It has been noted that there are significantly more bio active compounds in the extracts of *Piper betel* and *Triticum aestivum* Linn. When compared to the control medication, two of the discovered compounds catechin and chlorogenic acid with transferrin showed a greater binding affinity with the iron-binding receptor.

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CONFLICTS OF INTEREST

The author has no conflicts of interest.

CONTRIBUTIONS

Sonia Johri drafted the paper along with the interpretation of the data related to protein-protein interaction. Nabomita Paul wrote the manuscript and performed molecular docking along with protein-protein interaction network. Sonia Johri and Neha Khan compiled the review and preliminary studies. All authors approved the manuscript.

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