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Original Article

Molecular Docking, ADMET Analysis and Dynamics Approach to Potent Natural Inhibitors against Sex Hormone Binding Globulin in Male Infertility

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ABSTRACT

Objectives: The Sex Hormone Binding Globulin (SHBG) plays an important role in male infertility. **Methods:** The present research computationally emphases to SHBG protein with 47 natural phytocompounds using docking studies. **Results:** From the results showed the interactions between 1KDM protein with 47 phytocompounds, a natural compound chlorogenic acid showed the best glide docking XP score -7.255 kcal/mol and the binding energy value of -47.869 kcal/mol. Based on the result, the chlorogenic acid and target were run on MD simulations stable at 10 ns. **Conclusion:** Finally, this study concludes the chlorogenic acid is a suitable drug candidate for infertility.

Key words: Male infertility, SHBG, Phytocompounds, Molecular docking, ADMET property, MD simulations.

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INTRODUCTION

Infertility is a disease of the reproductive system which affects both men and women with practically parallel recurrence. It is a global phenomenon affecting an average of 10% of human reproductive age population.[1] Male infertility is affecting one in six couple in common[2] which interferes with the process of spermatogenesis and reduce sperm quality and quantity. Mostly, men are affecting this infertility disease due to coronary heart diseases, diabetes mellitus, chronic liver diseases, chronic smoking, and insufficient vitamins, few genetic factor intakes have been reported to cause deleterious effects on spermatogenesis.[3] Androgens plays a central role in the maintenance of normal spermatogenesis, if androgen levels are decreased, infertility could ensue.

Gonadotropins [luteinizing hormone (LH) and follicle stimulating hormone (FSH)] secretion of estrogen reduces at pituitary level resulting in decreased testicular function and reduction in testosterone production and intratesticular and serum testosterone levels. The balance between serum androgen and estrogens is essential for normal semen parameters.[4,5] There are few specify information about Sex hormone-binding globulin (SHBG) is a high molecular weight plasma protein that binds androgens and estrogens and plays a key role in maintaining the balance between unbound and bound sex steroids.[6]

If we consider deeper high -binding affinity, SHBG acts as a major part of steroids in the blood and any changes in SHBG levels effects the allocation and entrance of these molecules to target tissues. Besides natural steroid hormones such as dihydrotestosterone, testosterone, and estradiol, SHBG has also been shown to bind several EDCs including phthalates esters. Binding of the endocrine disrupting chemicals such as phthalate esters to SHBG in the body represents a potential way of interfering in the natural ligand and protein interactions and leads to harmful effect for the usual performance of the steroid target organs. Molecular modeling of zebra fish homolog of SHBG with several EDCs has been reported. In recent years, reported docking of many phthalates with androgen, progesterone, estrogen and peroxisome proliferating-activated receptors (PPARs). However, molecular modeling studies of phthalate esters with human SHBG are apparently not available. These are the information's about the infertility disease.[7,8,9]

MATERIALS AND METHODS

Molecular study was performed using different modules of Schrodinger.[10] The schematic representation describes the work flow of the study Figure 1 followed by detailed description in the subsequent sections.

Modeling platform

All computational analysis was carried out on Schrodinger suite device Maestro 10.2 version (ligprep, glide XP docking, grid genera-

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tion, free energy calculations, and ADME-toxicity and MD simulations). This software package programmed on DELL PRECISION T1700 workstation machine running on Intel (R) Core (TM) i5-4590 CPU processor with 8GB RAM and 240 GB hard disk with centos Linux as the operating system. The schematic representation describes the work flow of the study followed by detailed description in the subsequent sections.[11]

Biological data

In this study 47 bioactive molecules were selected against the target of SHBG. These bioactive molecules names and their medicinal plants were linsted in Table 1.[12-31] Later, this collected 47 bioactive molecules were retrieved from the chemical database.[32] The sex hormone-binding globulin (SHBG) receptor was obtained from Protein Data Bank PDB ID: 1KDM.[33]

Preprocessing and preparation of protein target structure

Protein X-ray crystal structures of SHBG was obtained from the Protein Data Bank after converted into PDB format with the help of Schrodinger software. The protein preparation is using by the tool of protein preparation wizard on Schrodinger suite. In general, protein is commonly occupied the water molecules. But, this process was evacuating those water molecules for increasing the entropy of target.[34,35]

Preprocessing and preparation of ligands

All the ligand molecules are prepared by the tool ligprep in Schrodinger.[36] Later these ligand molecules optimized on various ionization states, tautomer, stereo chemistries and ring conformations to adding molecules. It was using ligand rotatable bonds can move freely on further process.[37,38]

Molecular docking analysis

The Maestro suite[10] was used to perform molecular docking and utilized to prepare the input pdb file SHBG (PDB ID: 1KDM). Molecular docking uses the computational simultion predicts the ligand preferred orientation to a receptor when interact each other to form a higher stability complex. In this study Maestro 10.2 version tool was used to perform rigid flexible docking for predicting binding affinity, ligand efficiency and inhibitory constant. Glide Extra precision (XP) tool is used for the justification of suitable ligand molecule to the active site of specific target. The ligands being docked were kept flexible.[39,40]

Molecular dynamics simulations

MD simulation was performed using Macromodel Version9.0 (a Schrodinger module).[41] The OPLS_2005 force field was used for the energy calculation. Constant temperature was 300 K and in the integration step 1.0 fs was given. Run the MD simulations for complex structure. MD simulation with position restraints was carried out for a period of 4000 PS to allow the accommodation of the water molecules in the system. Finally, Root Mean Square Deviation (RMSD) was calculated for checking the stability of 1KDM protein with their native motion. All the coordinate file was saved every 1000 ps upto 4 ns and the result was analyzed by Scatter Plot.[42-44]

Estimation of ligand binding energy using Prime-MM-GBSA

The ligand binding energy of total 10 phytocompounds to inhibit SHBG was estimated using Prime MM-GBSA module in Schrodinger Suite 2014.[45] The total free energy of binding, dGbind (kcal/mol) is estimated by the software as:

$$\Delta G \text{ bind} = G \text{ complex} - (G \text{ protein} + G \text{ ligand})$$

Where in each energy term is a combination of G = MME (molecular mechanics energies) + GSGB (SGB solvation model for polar solvation) + GNP (nonpolar solvation) Coulomb energy, Covalent binding energy, Van der Waals energy, Lipophilic energy, Generalized Born electrostatic solvation energy, Prime energy, Hydrogen-bonding energy, Pi-pi packing energy, Self-contact correction.[46]We then used this score to rank the ligand-protein glide XP docked complex.[47]

ADME-Toxicity

ADMET (absorption, distribution, metabolism, excretion and toxicity) predictions for the top docking hits (47 natural bioactive compounds) were calculated by using the QikProp [48] module of Schrodinger suite (QikProp, version 3.0, Schrodinger, LLC, New York, NY, 2010) program (Schrödinger software) running in normal mode. QikProp generates physically relevant descriptors, the toxicity a ligand is considered important for the ligand to act as an effectual drug discovery of new drug development. These entire processes were used by Schrodinger software.[49]

RESULTS

Molecular docking

In this study, we intended to explore the overlaps SHBG inhibitory special effects of chlorogenic acid. In this protein sequence length is 177 amino acids and the resolution is 2.35 Å. These structures were to abolish water elements. A descriptive hydrogen atom was added to every inhibitor to assure that all of them were all-atom structures followed by energy minimization. After the protein preparation process is over, the protein is ready going with molecular docking. This molecular docking analysis has shown drug molecules potential and their hydrogen bond interaction where from the binding site of target. A total number of 10 natural compounds molecules in complex with SHBG protein were docked. Each ligand was docked with SHBG receptor that ligand molecules were produced docking score. The H-bond distance and their consequent glide energy were generated. And leading the docking score better drug for target molecules.[50] Based on the research finding which molecule is placed leading docking score with the good binding affinities. We justified, it is a suitable ligand for target.

In this analysis, a natural compound of chlorogenic acid has shown better results than other molecules. On the other hand, chlorogenic acid is a flavonoid nature. Moreover, this molecule is solving the male infertility problems and it was tested in both chemically and computationally.[51] This analysis outcome many compounds have received the docking score more than -4.0 Table 2. But, chlorogenic acid is received maximum value of docking score-7.225. Table 2.

Molecular interactions of chlorogenic acid with functionally important residues of SHBG

The SHBG protein interactions with ligands surfaces are controlled by a complex array of intermolecular interaction. Such interactions depend both on the specific interactions in the binding site as well as the non-specific forces outside the binding pocket. The protein- ligand interaction pattern between SHBG and chlorogenic acid was examined the site to which chlorogenic acid was binding. The chlorogenic acid was robustly interacting with diverse residues of the hydrogen bond (Side-chain, Back-chain) SER 180, TRP 170, SER 169, and ASP 168. In this interaction ASP 168 residues is involved in two times and the LYS 173 also interact n-cation Figure 2.

Analysis of docking results

The results of our docking analysis, pertaining to each ligand is presented below. The docking scores and binding affinities are presented in Table 2.

Chlorogenic acid

Through our molecular docking experiment, we found that chlorogenic acid efficiency. As a result chlorogenic acid had the best Glide Gscore

(-7.255 kcal/mol) and binding affinity score (-47.869 kcal/mol). Analysis of the docked complex showed that the residues Ser 180, Trp 170, Ser 169 and Asp 168 (2) were involved in hydrogen bonding with Chlorogenic acid. The residue Lys 173 was involved in hydration site with the ligand Figure 2a.

Trifluridine

Trifluridine had the second-best Glide G score (-5.417 kcal/mol) and binding affinity score (-46.574 kcal/mol). Analysis of the docked complex showed that the residues Trp 170 and Asp168 were involved in hydrogen bonding with Trifluridine Figure 2b.

Ellagic acid

Ellagic acid had the third best binding affinity score (-43.796 kcal/mol) with Glide G score of -4.805 kcal/mol. Analysis of the docked complex showed that the residues Ser 180 (2), Lys 173 and Asp 168 were involved in hydrogen bonding with Ellagic acid Figure 2c.

Kaempferol

Kaempferol had the fourth best binding affinity score (-41.101 kcal/mol) with Glide G score of -4.456 kcal/mol. Analysis of the docked complex

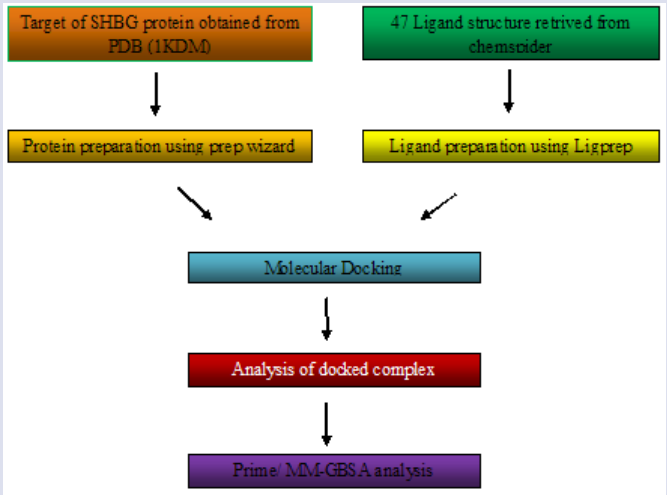

Figure 1: Schematic representation of the docking procedure and analysis.

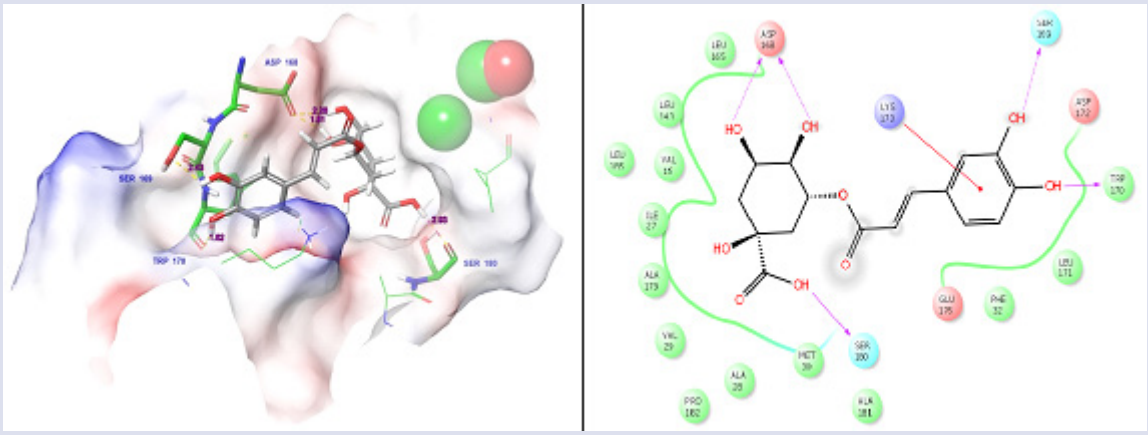

Figure 2a: Docked complex of 1KDM and Chlorogenic acid. (a). Dashed yellow line indicated hydrogen interaction n between target residues as well as ligand. (b). Structural view; blue solid straight line represented hydrogen bond back chain and blue dotted lines represented hydrogen bond side chain. Red colour indicated that ligand salt bridge interaction.

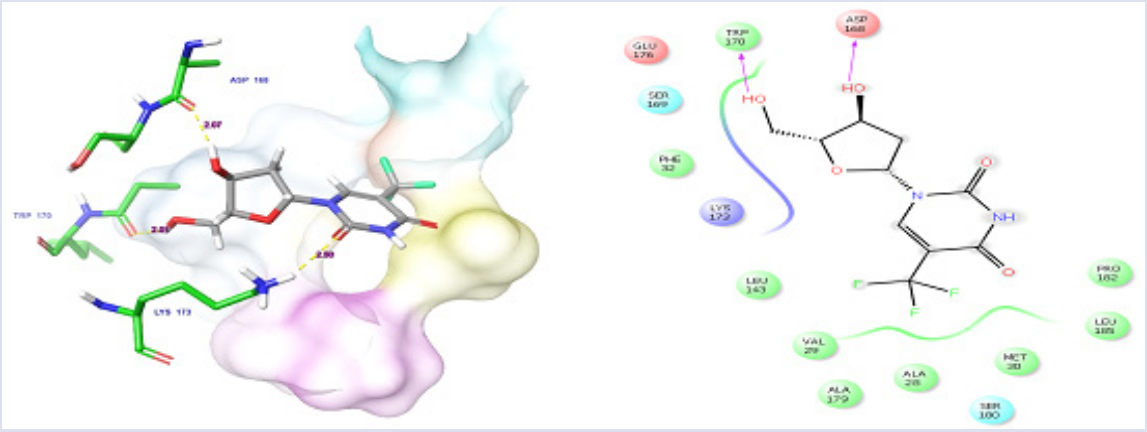

Figure 2b: Docked complex of 1KDM and Trifluridine (a). Dashed yellow line indicated hydrogen interaction n between target residues as well as ligand. (b). Structural view; blue solid straight line represented hydrogen bond back chain and blue dotted lines represented hydrogen bond side chain. Red colour indicated that ligand salt bridge interaction.

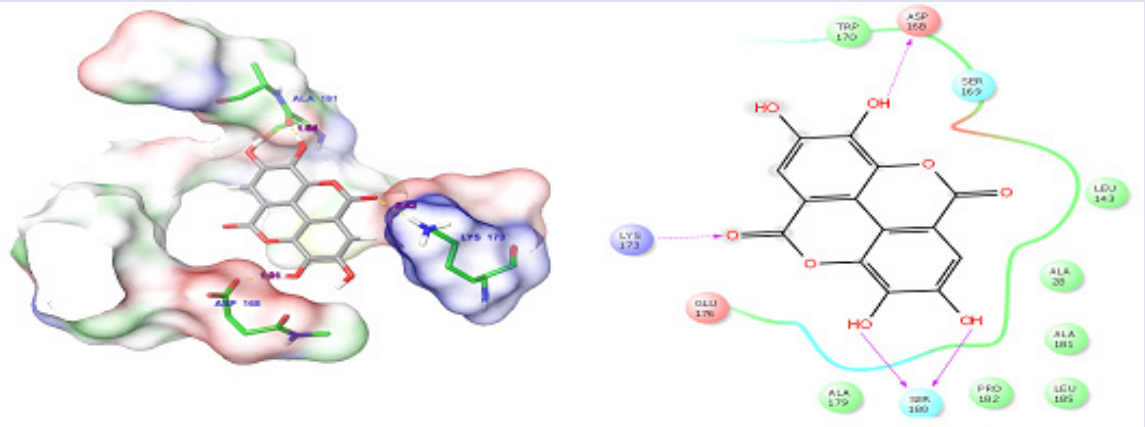

Figure 2c: Docked complex of 1KDM and Ellagic acid (a). Dashed yellow line indicated hydrogen interaction n between target residues as well as ligand. (b). Structural view; blue solid straight line represented hydrogen bond back chain and blue dotted lines represented hydrogen bond side chain. Red colour indicated that ligand salt bridge interaction.

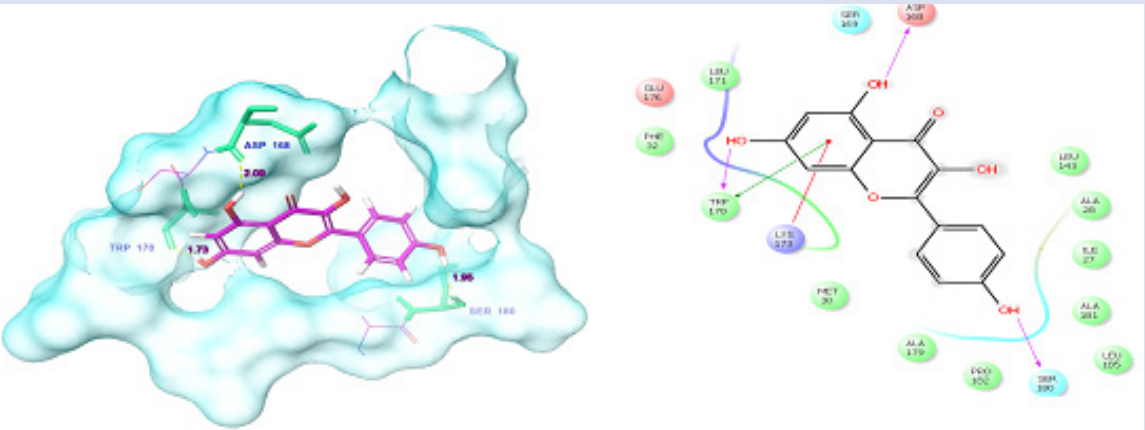

Figure 2d: Docked complex of 1KDM and Kaempferol (a). Dashed yellow line indicated hydrogen interaction n between target residues as well as ligand. (b). Structural view; blue solid straight line represented hydrogen bond back chain and blue dotted lines represented hydrogen bond side chain. Red colour indicated that ligand salt bridge interaction.

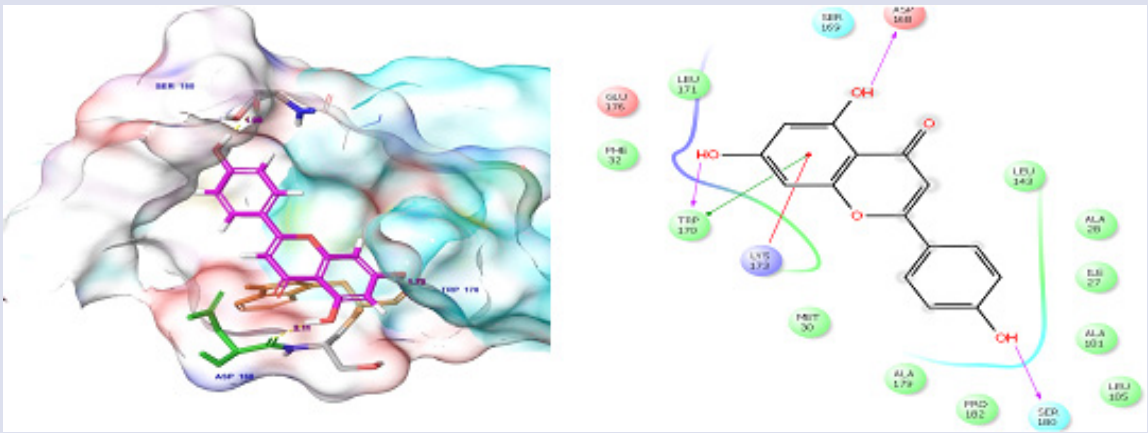

Figure 2e: Docked complex of 1KDM and Apigenin (a). Dashed yellow line indicated hydrogen interaction n between target residues as well as ligand. (b). Structural view; blue solid straight line represented hydrogen bond back chain and blue dotted lines represented hydrogen bond side chain. Red colour indicated that ligand salt bridge interaction.

showed that the residues Trp 170 (2), Asp 168 and Ser 180 were involved in hydrogen bonding with Kaempferol Figure 2d.

Apigenin

Apigenin had the second-best Glide G score (-4.149 kcal/mol) and binding affinity score (-32.849 kcal/mol). Analysis of the docked complex showed that the residues Sre 180, Lys 173, Trp 170, Asp168 were involved in hydrogen bonding with Apigenin Figure 2e.

Cinnamic acid

Cinnamic acid had the fourth best binding affinity score (-25.037 kcal/mol) with Glide G score of -3.658 kcal/mol. Analysis of the docked complex

Table 1: List of bioactive molecules and their source medicinal plants

S.No.	Compounds	Plant	Reference
1.	Chlorogenic acid	*Hibiscus sabadriffa*	[12]
2.	Trifluridine	*Calophyllum lanigerum*	[13]
3.	Ellagic acid	*Punica granatum*	[14]
4.	Kaempferol	*Moringa olifera*	[15]
5.	Apigenin	*Hibiscus rosa-sinensis*	[16]
6.	Cinnamic acid	*Glycine maxs*	[17]
7.	Pseudotropine	*Atropa belladonna*	[18]
8.	Scopoletin	*Euphorbia hirta*	[19]
9.	Rosmarinic acid	*Ocimum sanctums*	[20]
10.	2, 2, 4 - Trimethyl 3-pentanone	*Hibiscus rosa-sinensis*	[21]
11.	5-hydroxy-7, 8-dimethoxyflavanone	*Andrographis paniculata*	[22]
12.	5, 3'-dihydroxy-7, 8, 4'-trimethoxyflavone	*Andrographis paniculata*	[22]
13.	Urosolic acid	*Ocimum sanctum*	[20]
14.	Andrographidine	*Andrographis paniculata*	[22]
15.	gallic acids	*Punica granatum*	[23]
16.	Astringent	*Asparagus racemosus*	[24]
17.	Punicalagin	*Punica granatum*	[23]
18.	Cyanidin	*Hibiscus rosasinensis*	[25]
19.	2,6-Diisopropylnapthalene	*Euphorbia golondrina*	[26]
20.	Caffeic acid	*Syzygium caryophyllatum*	[27]
21.	Carvacrol	*Ocimum sanctums*	[20]
22.	Luteolin	*Euphorbia hirta*	[19]
23.	Linoleic acid	*Syzygium caryophyllatum*	[27]
24.	Linalool	*Ocimum sanctums*	[20]
25.	Gallic acid	*Hibiscus sabdariffa*	[12]
26.	Eucalyptol	*Euphorbia golondrina*	[26]
27.	Amylnitrite	*Hibiscus rosa-sinensis*	[21]
28.	Proline	*Hybanthus enneaspermus*	[28]
29.	Caryophyllene	*Euphorbia golondrina*	[26]
30.	4-Pentadecyne	*Ancistrocladus uncinatus*	[29]
31.	Myricetin	*Hibiscus sabdariffa*	[12]
32.	1 - iodoundecane	*Hibiscus rosa-sinensis*	[21]
33.	3,6-Octadien-1-ol,3,7-dimethy	*Ancistrocladus uncinatus*	[29]
34.	5-Caffeoylquinic acid	*Hibiscus sabdariffa*	[12]
35.	Octadecanoic acid	*Ancistrocladus uncinatus*	[29]
36.	2-Cyclopentylethanol	*Hibiscus rosa-sinensis*	[21]
37.	7-Tetradecenal	*Ancistrocladus uncinatus*	[29]
38.	Pinocembrin	*Euphorbia hirta*	[19]
39.	Ferulic acid	*Syzygium caryophyllatum*	[27]
40.	Quercetin	*Hibiscus sabdariffa*	[12]
41.	1-Fluorononane	*Ancistrocladus uncinatus*	[29]
42.	riboflavin	*Hibiscus rosasinensis*	[30]
43.	Xanthotoxol	*Syzygium caryophyllatum*	[27]
44.	Bartolome	*Ananas comosus*	[31]
45.	Quercetin	*Hibiscus rosa-sinensis*	[16]
46.	Caffeic acid	*Hibiscus sabdariffa*	[12]
47.	scoparone	*Euphorbia hirta*	[19]

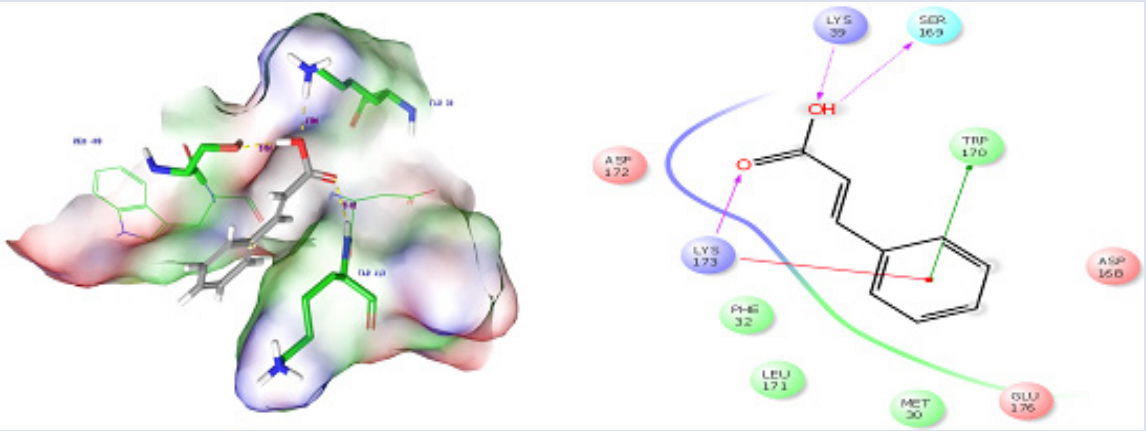

Figure 2f: Docked complex of 1KDM and Cinnamic acid (a). Dashed yellow line indicated hydrogen interaction n between target residues as well as ligand. (b). Structural view; blue solid straight line represented hydrogen bond back chain and blue dotted lines represented hydrogen bond side chain. Red colour indicated that ligand salt bridge interaction.

Table 2: Extra Precision Glide docking results with interacting amino acids in the active of SHBG

S.No.	Compound ID	Glide XP Docking score	Glide XP Energy (kcal/mol)	Glide XP Emodel	MMGBSA dG Bind (kcal/mol)	Interacting amino acids with distance [a]	HB
1.	1405788	-7.225	-43.783	-60.108	-47.869	Ser 180 (1.99), Ser 169 (2.43), Trp 170 (1.96), Asp 168 (2.28) and Asp 168 (1.81)	-3.9
2.	6020	-5.417	-31.783	-36.669	-46.574	Trp 170 (2.01), Asp (2.07)	-1.2
3.	4445149	-4.805	-34.388	-42.045	-43.796	Ser 180, Ser 180 , Lys 173 and Asp 168	-2.4
4.	4444395	-4.456	-34.046	-44.274	-41.101	Ser 180, Lys 173, Trp 170, Asp 168	-1.2
5.	4444100	-4.149	-32.849	-41.748	-38.841	Ser 180, Lys 173, Trp 170, Asp 168	-1.2
6.	8454	-3.658	-25.037	-32.715	-30.512	Lys 173, Trp 170, Ser 169, Lys 39	-0.6

[a]Residues involved in the Docking against SHBG receptor {the distance between the amino acid and ligand are calculated in Angstrom (Å)}.

Table 3: Qikprop Property of natural phytocompounds representatives

S.No.	Molecular Weight Da	Volume	SASA	Acceptor HB Groups	Donor HB Groups	Number of Ring Atoms	QPlogPw (-2to 6.5)	% Human Oral absorption
1.	354.313	1016.673	576.52	9.65	6	12	20.326	1
2.	296.203	803.413	485.172	8.6	3	11	14.743	2
3.	302.197	771.185	455.237	8	4	16	16.767	2
4.	286.24	843.244	504.763	4.5	3	16	12.311	3
5.	270.241	825.673	496.62	3.75	2	16	10.254	3
6.	148.161	565.799	366.827	2	1	6	5.69	3

showed that the residues Lys 173, Trp 170, Ser 169, Lys 39 were involved in hydrogen bonding with Cinnamic acid Figure 2f.

Molecular dynamics simulations

The molecular dynamics simulation was carried out for the protein SHBG and chlorogenic acid. For evaluate the structural constancy of those molecules with the help of Desmond. The final trajectory files were taken for calculating the RMSD of the complex structures. At the same time as running MD simulation for SHBG protein and chlorogenic acid for 10 ns, the RMSD (Root Mean Square Deviation) plot shows the stability of the complex structures. The period and the constant potential energy stable at 1.2 ns to 10 ns. In addition, when performing the simulation for 10 ns, and it makes the stability of the complex structure during the entire simulation time up to 10 ns Figure 3.

ADMET profiling

In the beginning stage of drug discovery physico-chemical indicators were used to find the vital properties affecting the biological functions (ADME) Table 3. There are some important measured physico-chemical properties such as permeability, solubility, lipophilicity, integrity and stability.[52] But the concept of ADME has been expanded by toxicity.[53] At the initial stage of drug discovery not only the several end points related to potential hazardous effects. Right from the beginning of disclosure strategy has been utilized to give a precise expectation of pharmacokinetic properties for moment ADMET.[54]

DISCUSSION

Similarly, Ishfaq *et al.*[55] reported that the compound dimethyl phthalate is shown superior docking score with the target of SHBG. Earlier, many

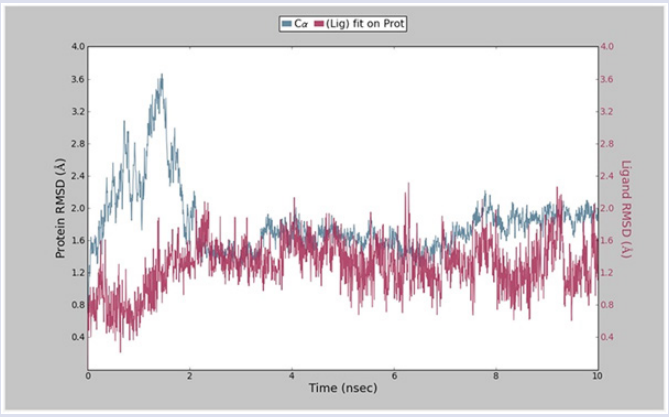

Figure 3: The root mean square deviation (RMSD) is used to measure the average change in displacement of a selection of atoms for a particular frame with respect to a reference frame. It is calculated for all frame in the trajectories.

researchers have been analyzed this molecular docking to different disease-causing receptor proteins to predicting various bioactive molecules respectively[56,57]. End of the outcome validation all the phytocompounds were validated by the binding mode of the target. The suitable ligand molecules have filtered based on the binding affinities of ligand to target amino acid residues. Binding affinities shows the contribution of ligand from target and strongly rely on the flexibility of receptor.

CONCLUSION

As a result of this computational experiment Phytocompound of the Chlorogenic acid has shown efficient docking score and effective binding affinities. Hence, we concluded that the chlorogenic acid may be a suitable potential to the SHBG stimulation. Based on this finding, we suggested that chlorogenic acid bioactive molecule used for further drug development process. And, this study will be addressed to further drug processing analysis.

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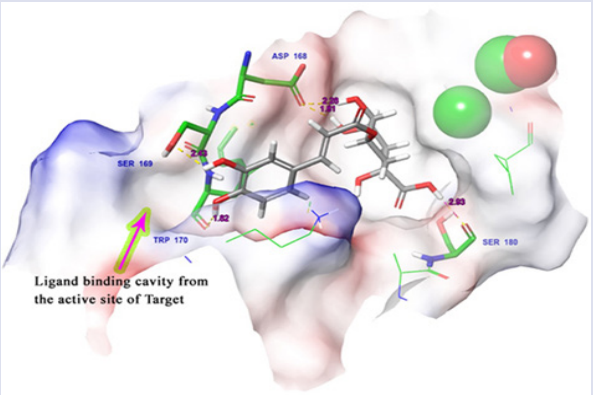
GRAPHICAL ABSTRACT



SUMMARY

- Sex Hormone Binding Globulin (SHBG) is involved to binds the androgens and estrogens in mammalian. It plays very essential role to safeguard the sex steroids between bound and unbound. Generally, the male infertility affects one in six couple in world which holds up with the development of spermatogenesis and it decreases the quality and quantity of sperm production. Commonly, people are spoiled their sperm production capacity especially male by the reason of certain mental and physiological illnesses which includes coronary heart disease, diabetes, chronic disease, etc. Spermatogenesis also caused by some genetic factors. Traditionally, the medicinal plants are having lots active primary and secondary metabolites which also act as physiological function into the human body especially reproductive system in both male and female.

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