ORIGINAL RESEARCH

Amentoflavone–A Probable Candidate for Drug Development

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ABSTRACT

Molecular docking is one of the most popular and user friendly computational technologies that helps in investigating, interpreting, explaining and identifying the molecular properties of a drug or ligand. In the present investigation, two ligands were tested against six receptor proteins that have pathological significance. The ligands were the synthetic drug, tamoxifen (an oral tablet for cancer treatment), and the test drug Amentoflavone (a biflavonoid reported to be present in two species of *Biophytum*). The target proteins (PTP1B, hPPARγ, iNOS, VEGF, VEGF2, and VEGFR2) selected for the present study, were retrieved from Protein Data Bank. During the molecular docking studies, the measure of interaction between the proteins and ligands were performed using the LibDock program (the score ligand poses protocol) from Discovery Studio, version 4.0 (Accelrys, San Diego, CA, USA) by calculating the libdock score. The present study results showed that the highest libdock score was between the protein PTP1B and amentoflavone (139.48), which was greater than the highest libdock score for the synthetic drug, tamoxifen (122.33). For tamoxifen, the libdock score was highest for iNOS. The number of hydrogen bonds, the absolute energy, bond type, bond distance and information about the amino acids involved in docking were calculated. It appears that the tested drug, amentoflavone has a greater interaction, revealing its significant role in pathological situations especially cancer and may be chosen as a candidate drug after conducting well-designed *in vitro* and *in vivo* studies. The present study reveals the utility of amentoflavone against these specific receptor proteins and may be considered a lead compound for drug development.

Keywords: Docking, Amentoflavone, Tamoxifen, Protein Data Bank, PubChem, LibDockscore

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INTRODUCTION

From very early times, herbal drugs served as an effective cure against common diseases. However, lack of proper authentication and scientific validation deterred their popularity. Recent advances in refinements in drug design, processing, and development has given them due importance. Such strategies would enhance the chances of an effective and safe cure to mankind.

To date, a large number of lead molecules have been identified from medicinal herbs. These are being utilised individually or in combinations for developing effective novel drugs. However, evaluating their efficacy remains a big challenge as it requires wet-lab experiments, a lot of time, money and manpower. A preliminary screening of such myriad compounds against specific receptor proteins on disease target sites by computer-aided drug design (CADD) will considerably reduce the time required for wet lab experiments and thus speed up the development of potential drugs for the corresponding maladies.

Molecular docking screens small molecules by orienting and scoring them in the binding site of a protein. It can be thought of as a "Lock and Key theory." This "ligand-based Screening Method" involves interactions of a small organic molecule having drug-like property with a target protein through intra or inter-molecular binding[1] In short, *in silico* molecular docking is a powerful technique that plays a key role in structure based drug designing.

In the present investigation, two ligands were tested against six receptor proteins, having pathological significance. One of the ligands chosen was the synthetic drug, Tamoxifen (Nolvadex®)(commonly consumed as an oral tablet for the treatment of cancer) and the other, the test drug, amentoflavone, [a biflavonoid reported to be present in two species of *Biophytum viz., B. veldkampii* Shanavas et al. and *Biophytum reinwardtii* (Zucc.) Klotzsch.[2]

MATERIALS AND METHODS

Protein Preparation

The six target proteins were retrieved from Protein Data Bank (www.rcsb.org) and crystallographic water molecules were removed from the protein. The retrieved file contained

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structural information of the macromolecules determined by compound detection techniques such as X-ray crystallographic and NMR-methods. Proteins (with their PDB ID) selected for the present study are shown below (Table 1).

Preparation of Ligand

The structure of synthetic ligand (Tamoxifen) and the test ligand, amentoflavone were downloaded in .sdf format from PubChem database.[3]

Tamoxifen (Nolvadex®) (Pubchem ID-2733526)

An oral medication commonly used for the treatment of breast cancer. Tamoxifen is used as endocrine therapy for breast cancer in pre- and post-menopausal women as it interferes with estrogen activity.[4] Some of the most common side effects of tamoxifen are blood clots, strokes, uterine cancer, and cataracts. The side effects make this drug unsuitable for treatment. A better alternative for tamoxifen is sought.

Amentoflavone (Pubchem ID - 5281600)

A bioactive biflavonoid, shown to possess antioxidant,[5] anti depressant.[6] anti-inflammatory,[7] antiviral,[8] analgesic[9] and anti-cancer activities.[10]

Protein–ligand Docking Analysis

Molecular docking was carried out in Ligand fit of Accelrys Discovery Studio software 4.0 (Accelrys, San Diego, CA, USA), a structure based designing software.

The binding sites of the protein were predicted using 'find cavities' from the 'receptor site' parameter of the tool. The determination of the ligand binding affinity was calculated using Dock scores. The dock score for each ligand was calculated by the software itself. The numbers of Hydrogen bonds involved in the interaction along with amino acids involved in the hydrogen bonding and distance between the hydrogen bonds were also estimated using Accelrys Discovery Studio software.

Table 1: Name of the proteins selected for the docking study

Sl. No	*Name of proteins*	*PDB ID*
1	PTP1B	1Q1M
2	hppARγ	3VI8
3	iNOS	1M9K
4	VEGF	1FLT
5	VEGF2(VEGF-C)	2X1X
6	VEGFR2	1Y6A

RESULTS

The molecular docking analyses of six target proteins (PTP1B, iNOS, VEGF, VEGFR2, hppARγ, VEGF2) with the synthetic drug tamoxifen and the natural compound, amentoflavone were performed using Libdock protocol of Discovery studio 4.0.

Docking studies on these selected proteins displayed various parameters such as i) the number of hydrogen bonds, ii) the absolute energy, iii) bond type and bond distance and iv) information about the amino acid interactions between proteins and ligands. The measure of interaction was determined by calculating the libdock score. The results showed better binding capacity between the protein PTP1B and amentoflavone with the best libdock score (139.48) when compared to that between the other proteins and amentoflavone. The dock score order for amentoflavone is as given: PTP1B (139.48) > iNOS (131.97) > VEGF (126.24) > hppARγ (118.21) > VEGFR2 (115.19) > VEGF2 (109.53). All the values were higher for amentoflavone (>100). The libdock score for amentoflavone was even greater than the synthetic drug,

Tamoxifen. Tamoxifen had the highest libdock score (122.33) for the protein, iNOS, followed by VEGF > VEGF2 > hppARγ > VEGFR2>PTP1B in that order. Of the six proteins docked, PTP1B exhibited the highest number of hydrogen bonds (8). Numbers of hydrogen bonds varied from two to eight. Different types of hydrogen bonds such as conventional hydrogen bonds, Pi-donor hydrogen bonds, and carbon hydrogen bonds are involved in the protein interactions. Details of docking results are expressed in Tables 2 and 3 and Figures 1-6.

DISCUSSION

Molecular docking provides information about the ligand-protein interaction through force fields by orientation and translation. The orientation directly refers to the strength of

Table 2: Details of protein interactions with amentoflavone and tamoxifen

Sl. No	*Proteins*	*Ligands*	*Absolute energy (Kcal/mol)*	*Libdock score*	*Number of hydrogen bonds*
1	PTP1B	Amentoflavone	80.2572	139.48	8
		Tamoxifen	90.9181	95.87	4
2	iNOS	Amentoflavone	81.8387	131.97	4
		Tamoxifen	100.408	122.33	4
3	VEGF	Amentoflavone	81.8387	126.24	2
		Tamoxifen	25.1571	121.92	5
4	hppARγ	Amentoflavone	81.1371	118.21	3
		Tamoxifen	99.512	97.855	6
5	VEGFR2	Amentoflavone	80.2572	115.197	2
		Tamoxifen	85.5335	97.5083	3
6	VEGF2(VEGF-C)	Amentoflavone	80.2572	109.53	2
		Tamoxifen	32.0747	103.33	6

Table 3: Details of protein interactions with amentoflavone and tamoxifen

Sl. No	*Name of proteins and Ligands*	*Aminoacids and their residues*	*Bond category and bond distance (angstrom)*	*Bond type*
1	PTP1B with amentoflavone	A:ARG24:NE-5281600:O6 A:ARG221:N-5281600;O9 A:ARG221:NH-5281600:O7 A:LN266:NE2-5281600:09 5281600:H41-A: ASP48: O 5281600:H42-A: ASP48: O A:GLN262:NE2-5281600 A:GLN262:NE2-5281600	Hydrogen bond 1.5815 -3.4784	Conventional hydrogen bond and Pi-donor hydrogen bond
	PTP1B with tamoxifen	A:ALA217:N-2733526:O1, 2733526:H44-A:ASP181:OD1 2733526:H58-A:GLN266:OE1 A:TYR46:OH-2733526	Hydrogen Bond 2.5287 -3.7934	Conventional hydrogen bond, carbon hydrogen bond and Pi-donor hydrogen bond
2	iNOS with amentoflavone	A:ARG365:NH2-5281600:O9 5281600:H44-A: TRP447: O 5281600:H44-A: VAL449: O A:CYS184:SG-5281600	Hydrogen Bond 2.1793 -3.2982	Salt bridge conventional hydrogen bond and pi-donor hydrogen bond
	iNOS with tamoxifen	A:TP356:N-273356:O1, 2733526:H29-A:TRP356: O, A:GLY355:CA-2733526:O1, 2733526:H54-A:TRP356: O	Hydrogen Bond 2.1870 -3.0614	Conventional hydrogen bond and carbon hydrogen bond
3	VEGFwith amentoflavone	5281600:H45- X: ARG224: O V:SER50:CB- 5281600:O8	Hydrogen bond 1.600,3.1099	Conventional hydrogen bond and carbon-hydrogen bond
	VEGFwith tamoxifen	W:GLU64:;N-23682211:08 W:GLU64:N-23682211:010 23682211:H27V:ASP34:OD1 23682211:H32-V:ASP34:OD2 23682211:H33- W:GLU64:OE2	Hydrogen bond 1.6544 -3.0322	Conventional hydrogen bond and carbon-hydrogen bond
4	hppARγ with amentoflavone	A:ASN219:ND2-5281600:O6 5281600:H45-A:MET355:SD A:VAL332:CA-5281600:O4	Hydrogen Bond 2.7235 -3.4276	Conventional hydrogen bond and carbon hydrogen bond
	hppARγ with tamoxifen	A:TYR334:N-2733526:O1 273356:H29-A: THR279: O 273356:H55-A:TYR334:OH A:CYS275:SG-2733526 A:CYS276:SG-2733526 A:ALA333:N-2733526	Hydrogen Bond 2.6836-3.9649	Conventional hydrogen bond, Pi-donor hydrogen bond and carbon hydrogen bond
5	VEGFR2 with amentoflavone	5281600:H45 –A:GLU883:OE2 A:PHE916:CA – 5281600:O6	Hydrogen Bond 2.2418 -3.7333	Conventional hydrogen bond and carbon hydrogen bond
	VEGFR2 with tamoxifen	2733526:H29 – A: CYS917: O 2733526:H44 – A: CYS917: O 2733526:H46 – A: CYS917: O	Hydrogen bond 1.8154 -2.9359	Conventional hydrogen bond and carbon hydrogen bond
6	VEGF2 with amentoflavone	E:CYS156:SG -5281600 E:CYS156:SG -5281600	Hydrogen bond 2.9934 -3.3138	Pi-donor hydrogen bond
	VEGF2 with tamoxifen	E:ALA147:N –23682211:N R:ASP276:N –23682211:O9 23682211:H2 – E: THR150: O 23682211:H27–E: THR150:O 23682211:H30R: ASP276:OD1 23682211:H31 –E: GLY141: O	Hydrogen bond 2.5472 -3.2140	Conventional hydrogen bond and carbon hydrogen bond

bond association or bond affinity between these two molecules and is also known to predict the scoring functions. The scoring function is a mathematical method of virtual screening that predicts the non-covalent interaction between the two molecules after their docking.[1] Normally, a small organic molecule, drug molecule, or ligand (drug liking property) and a biologically active protein (target molecule of the drug-target protein or receptor-derived from PDB) are used for the experiment. The scoring function directly influences the biological activity of that relevant docked molecule.

The main focus of molecular docking is to recognize the optimizing conformation and relative orientation of proteins and ligands, which minimized the system's free energy and thereby predicts the best fitting area to define the best pose of a ligand. The best pose of the ligand reveals the comparatively better biological activity of that compound. Hydrogen bonds

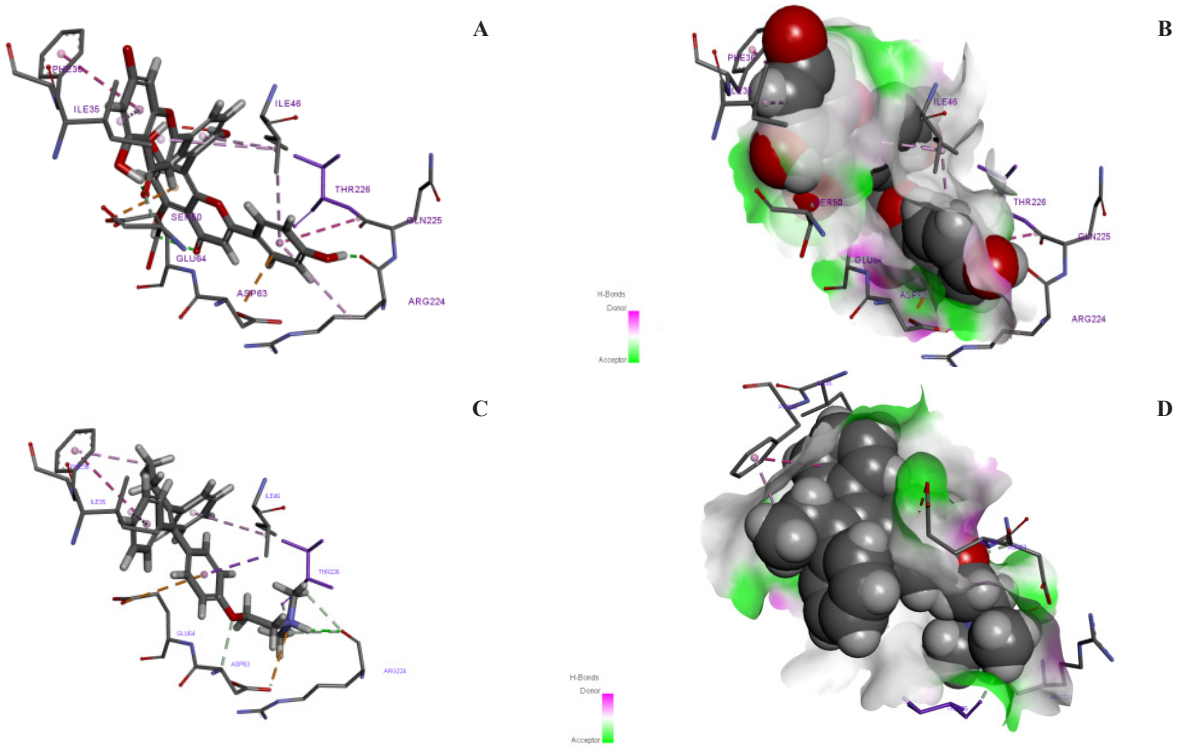

Figure 1

A. A close view of hydrogen bonding interaction between VEGF protein and Amentoflavone
B. Docked image of Amentoflavone with VEGF protein
C. A close view of hydrogen bonding interaction between VEGF protein and Tamoxifen
D. Docked image of Tamoxifen with VEGF protein

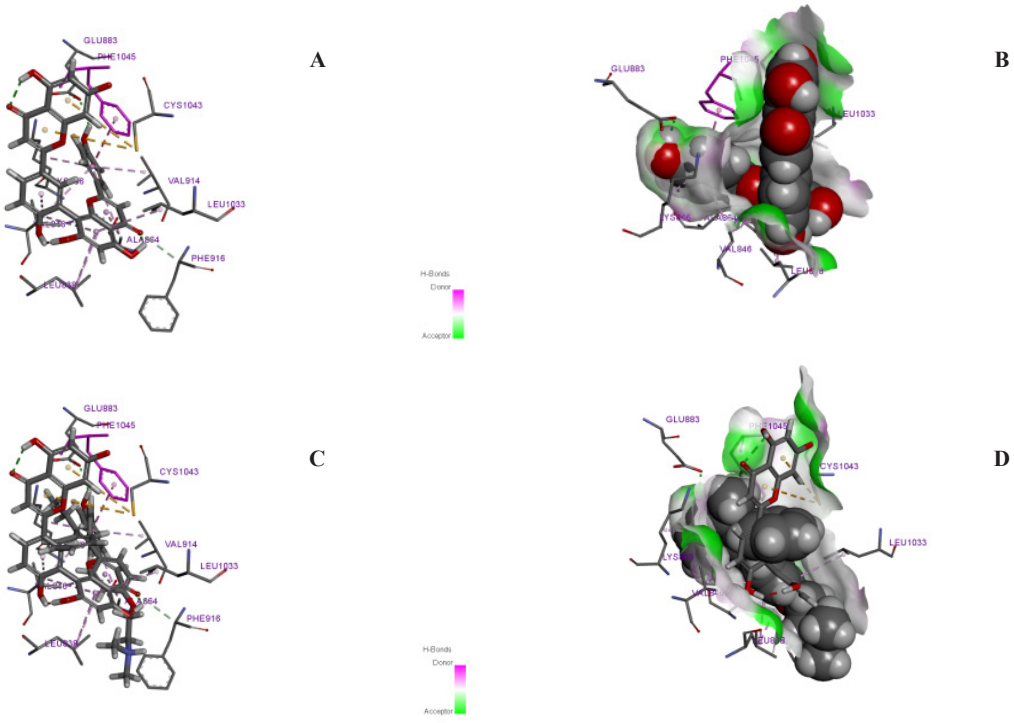

Figure 2

A. A close view of hydrogen bonding interaction between VEGFR2 protein and Amentoflavone
B. Docked image of Amentoflavone with VEGFR2 protein
C. A close view of hydrogen bonding interaction between VEGFR2 protein and Tamoxifen
D. Docked image of Tamoxifen with VEGFR2 protein

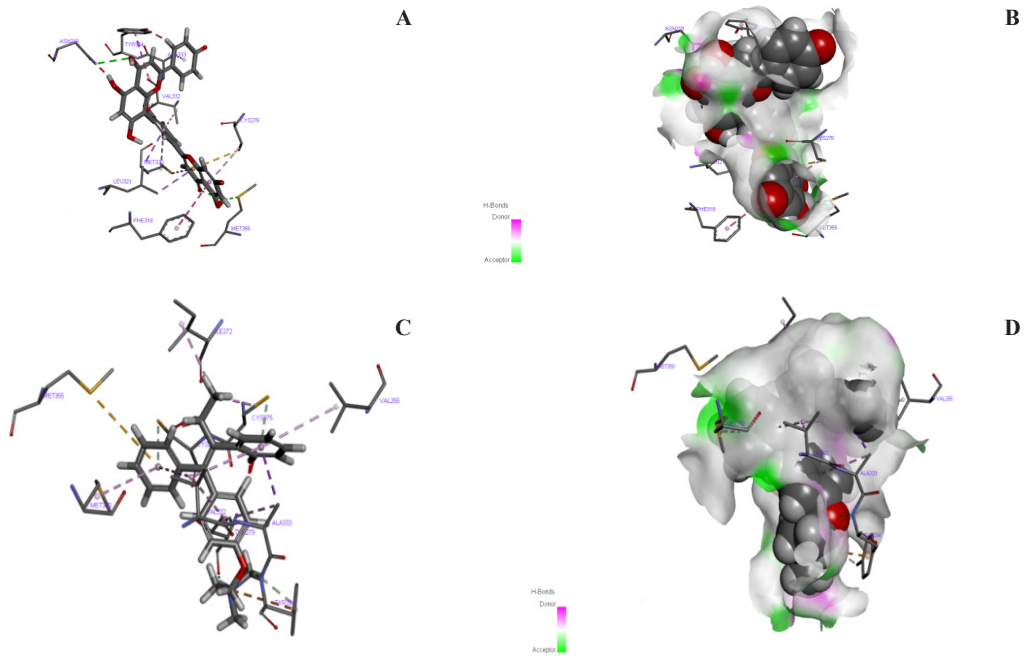

Figure 3

A. A close view of hydrogen bonding interaction between hppARγ protein and Amentoflavone
B. Docked image of Amentoflavone with hppARγ protein
C. A close view of hydrogen bonding interaction between hppARγ protein and Tamoxifen
D. Docked image of Tamoxifen with hppARγ protein

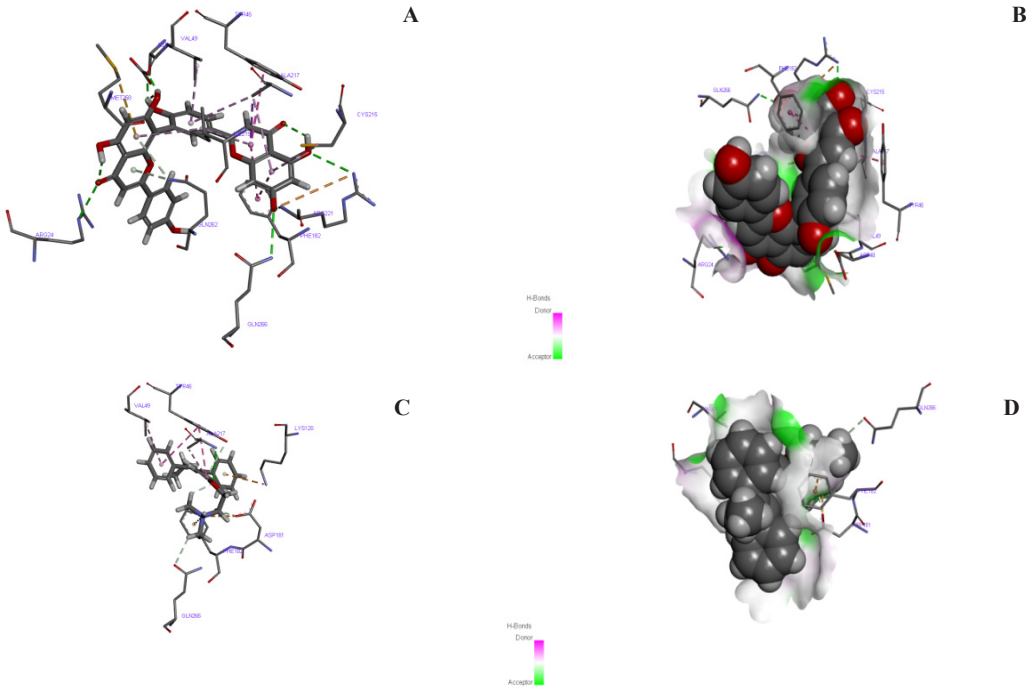

Figure 4

A. A close view of hydrogen bonding interaction between PTP1B protein and Amentoflavone
B. Docked image of Amentoflavone with PTP1B protein
C. A close view of hydrogen bonding interaction between PTP1B protein and Tamoxifen
D. Docked image of Tamoxifen with PTP1B protein

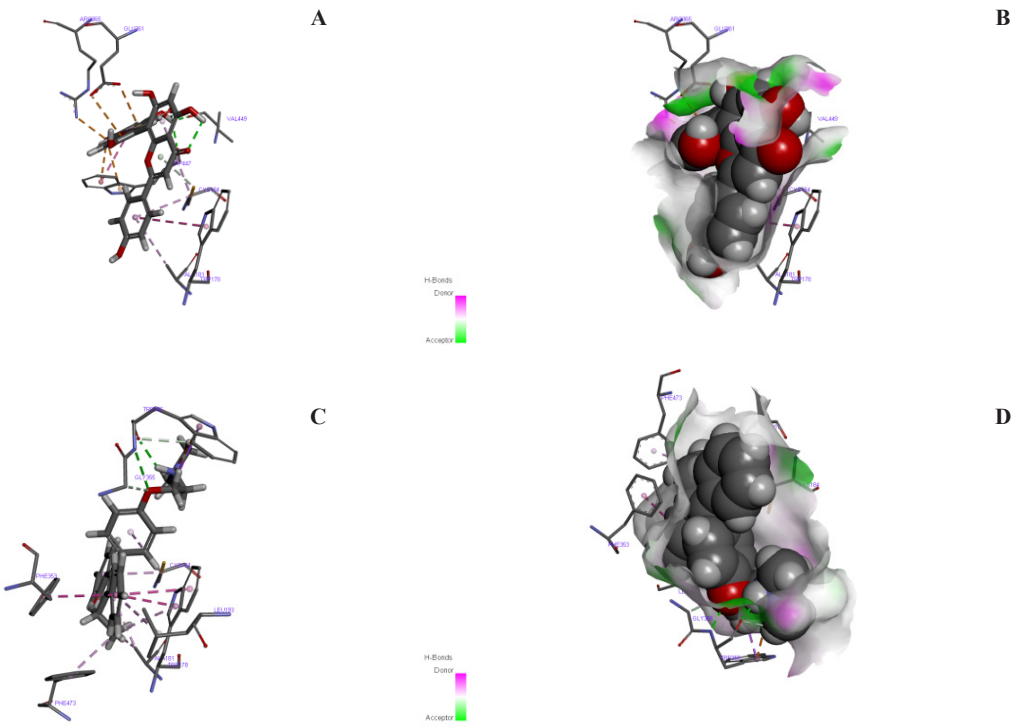

Figure 5

A. A close view of hydrogen bonding interaction between iNOS protein and Amentoflavone
B. Docked image of Amentoflavone with iNOS protein
C. A close view of hydrogen bonding interaction between iNOS protein and Tamoxifen
D. Docked image of Tamoxifen with iNOS protein

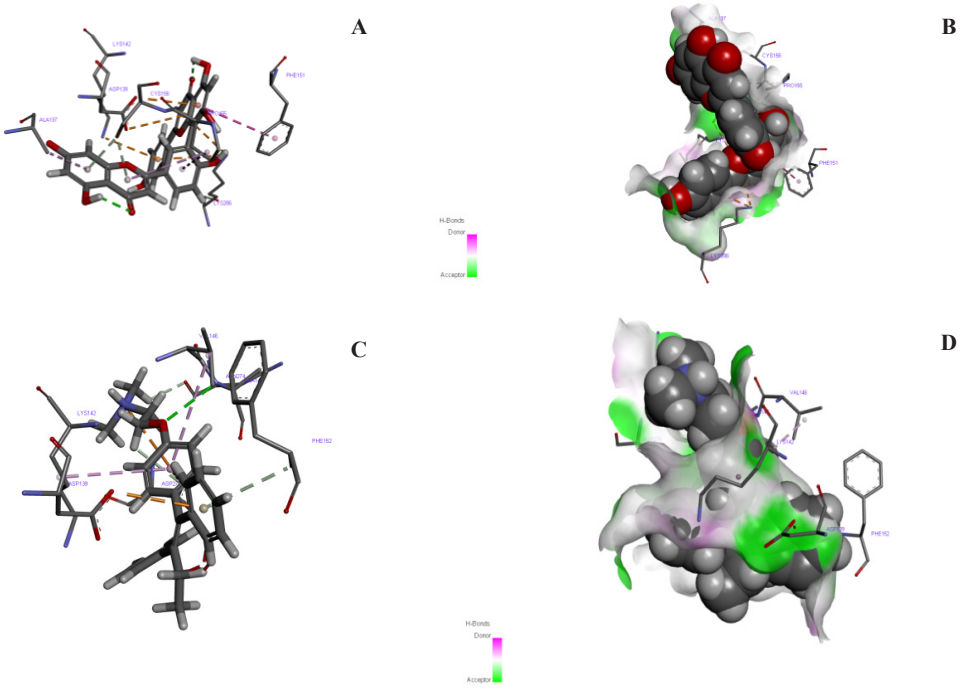

Figure 6

A. A close view of hydrogen bonding interaction between VEGF2 protein and Amentoflavone
B. Docked image of Amentoflavone with VEGF2 protein
C. A close view of hydrogen bonding interaction between VEGF2 protein and Tamoxifen
D. Docked image of Tamoxifen with VEGF2 protein

Table 4: Summary of the role of proteins included in the docking studies with amentoflavone and tamoxifen

Sl. No	*Name of Protein*	*Protein Super family*	*Disease*	*Receptors induced*	*Reference*
1	PTP 1B	Protein tyrosine phosphatase superfamily	Ovarian, gastric, prostrate and breast cancer, Type II Diabetes, Obesity	Receptor Tyrosine Kinases (RTKs)	[12,13,14]
2.	iNOS	Inducible nitric oxide synthase superfamily	inflammation, infection, neoplastic diseases, liver- cirrhosis, diabetes	LPS, IL-1, TNF-α and INF-γ	[15,16]
3	VEGF	Cystine-knot superfamily	Cancer, atherosclerosis, arthritis, diabetic retinopathy	FLT1, KDR,NRP1	[17,18,19]
4	hppARγ	Nuclear receptor superfamily	Obesity, diabetes, and cancer	CD36, EDF1,MED1,PPARGC1À,EP3OO	[2,21]
5	VEGFR2	Cystine-knot superfamily	Cancer, proliferation, metastasis and diabetic retinopathy	Receptor Tyrosine Kinases	[22]
6	VEGF-2(VEGF-C)	Cystine-knot superfamily	Lymphedema, metastasis vascular disease in the retina of the eye and other parts of the body	Receptor Tyrosine Kinases (VEGFR2 and VEGFR3) Neuropilin (NRP)-1, NRP-2 and integrin $\alpha 9\beta 1$	[23,24]

are one of the important factor that contributes to the stability of protein-ligand binding interactions during docking.[11] In the present study, different types of hydrogen bonds are involved in interactions (Table 3).

The present study results showed that a good interaction occurs between the protein PTP1B and amentoflavone (with best libdock score as 139.48) and showed more binding capacity than the other proteins. This was followed by iNOS, VEGF, hppARγ, VEGFR2, respectively. Among all the docked proteins, amentoflavone exhibited the libdock score > 100. Similarly, among all the proteins, amentoflavone had a greater libdock score than even the synthetic drug, tamoxifen, which appears quite interesting.

The significance of the results is evident from the importance of the proteins in human metabolism. The role of proteins included in the docking studies with amentoflavone and tamoxifen is detailed below (Table 4).

The results of the present study indicate that, amentoflavone has good interaction and inhibitory effect against the chosen cancer causing proteins. Interestingly, amentoflavone was even more effective than the synthetic drug, tamoxifen. Thus, it is evident that amentoflavone, may be chosen as a candidate drug for combating such pathological situations after conducting well- designed *in vitro* and *in vivo* studies.

CONCLUSION

Docking reactions of amentoflavone against cancer causing receptor proteins suggests that amentoflavone might be considered as a lead compound for the development of potentially useful drugs.

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