

Drug Development for PCGF2 Protein, Involved in Formation of Human Breast Cancer by Polyphenols and Their Derivatives Extracted from *Cowania maxicana*

Jawaria Khan^{*}, Ardas Masood, Asma Noor, Muhammad Imran Qadir

Institute of Molecular Biology and Biotechnology, Bahaudin Zakariya University, Multan, Pakistan

E-mail address:

jiakhan77777@gmail.com (J. Khan)

^{*}Corresponding author

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Abstract: In women, the most commonly found cancer is breast cancer. PCGF2 (polycomb group RING finger protein 2) was found to be one of the reasons that cause breast carcinoma in women. Ring finger protein causes formation of multiprotein complexes and mediates interactions between different proteins. The polyphenols, extracted from *Cowania maxicana* and their derivatives were found to have anti proliferative activities. They showed greater efficiency and specificity towards the target protein PCGF2 (polycomb group RING finger protein 2).

Keywords: Breast Cancer, PCGF2, Polyphenols, *Cowania maxicana*, Pedunculagin

1. Introduction

A tumor that is present in the area of breast in the humans is called adenocarcinoma. Breast cancer is one of the most common cancers occurring in human and cover 18% of all cancers and nearly 1 in 3 cancers diagnosed among women in the United States (DeSantis et al., 2011).

There are many methods to treat cancer e.g. surgery, radiation therapy and chemotherapy. The clinical way of a patient having breast carcinoma stays tricky to predict, as tumors of apparently homogenous morphological characteristics still differ in response to therapy and have different results (Alizadeh et al., 2001; Rakha et al., 2007). The clinical course of a patient with breast carcinoma remains difficult to predict, as tumors of apparently homogenous morphological characteristics still vary in response to therapy and have divergent outcomes. Chemo prevention is another method to treat cancer. Using natural or manmade products to treat cancers is called cancer. It is considered along, proficient and reversible process to treat invasive and multistage cancers (Kuo et al., 2005). Chemoprevention has been studied a lot in recent years. *Cowania maxicana* (rosaceae) is found in North America. Its

leaves and branches showed antitumor activity by strongly inhibiting the PCGF2 protein (also known as ring finger protein 110) involved in formation of breast adenocarcinoma. This plant has other medicinal properties. It has been used against respiratory disease and cough. Mixed extract of herbs or plants might contain different chemo preventive chemotherapeutic compounds with more than one mechanism of action (Hu et al., 2002). Recent studies show that rosaceous plants have an abundant amount of polyphenols that have various biological activities. I have examined the polyphenols and their derivatives of this plant. In this paper I have characterized polyphenols extracted from *Cowania maxicana* and its derivatives and checked their antitumor activity by examining their inhibitory effect on PCGF2.

Phenotypic behavior of cancer cells is not only controlled by cell autonomous signals, but it is also affected by adjoining stromal cells (Barbarettani et al., 2006). Ring finger is a pattern of conserved histidines and cysteines that synchronize two zinc atoms in a cross-brace system, a ligation scheme distinct from those of classical zinc finger 1

and 2 (Yin et al., 1999). Ring finger protein causes formation of multiprotein complexes and mediates interactions between different proteins (Hamamoto et al., 2004). RING finger plays major role in the binding to promoter specificity protein 1 (sp1) (Brindha et al., 2009) even though breast cancer death rates have been lowered to 34% since 1990, not all parts of the population had an advantage from this decrease (DeSantis et al., 2014). Treatment of cancer is along and tiring procedure. It is an expensive, inconvenient and not easily available everywhere, but the main problem is harmful side effects caused by cancer drugs (Hilakivi-Clarke et al., 1994). For example, it is considered that if chemotherapy is carried out for longer periods, it makes the immunological defense system of the patient's body weak which may result in him being in danger of more diseases and infections by making his body susceptible to them. RING- finger motif in BRCA 1 is part of a larger N-terminal structural domain. Families that have a genetic history of ovarian and breast cancer have many mutations at this site (Ameyar et al., 1998).

2. Materials and Methods

In the field of biotechnology and pharmacy drug designing is the method by which drugs are found and made. It is a process by which drugs are formed on the basis of design and on the basis of what the drug targets are, using bioinformatics. Drug developing is not an easy process. It requires time, patience, and expertise (Yaminian and Vijjulatha, 2008). Drug designing starts with the finding of a right target compound responsible for causing disease (Zyad et al., 2008). Drug designing and drug formation is very important for human health. Its success depends upon the expertise and new techniques by using both biological and chemical research. For this process computational method is adopted. It is usually joined with structural information obtained from and nuclear magnetic resonance investigation and macromolecular crystallography. Recent studies have helped us to develop large libraries of possible bioactive compounds by combinational methods, which will play an important role in drug discovery (Agrafiotis et al., 2008).

3. Software Required

1. Pymol
2. Autodock
3. Discoverystudio4.1
4. Autodock vina
5. Medchem.

4. Disease Selection

A human body undergoes many complex biochemical procedures which make and recycle different compounds in a well coordinated and in a balanced way. A disease is basically produced when the rear changes in these biochemical pathways (Yu et al., 2007). When developing a

drug we first need to understand the basic biological nature and symptoms caused by a disease to understand whether it is caused by an antigen which may be any infectious agent like bacteria or virus, a synthetic compound or a protein (Tisdale, 2004). When we are selecting a disease for development of a drug, there are many factors involved like pathogenesis of a disease, evolution of a disease, involved proteins, its death rate, how many drugs are already available, their side effects and their efficiency, etc.

5. Target Molecule Prediction

Target molecule means the target protein which is a causative agent of the disease we want to form the drug against (McInnes, 2007). The cellular targets of many drugs are generally proteins. The drugs act by binding to receptor molecules (Briscoe, 2009). It will either increase or stop its activity (Dobson and Barnett, 2008). In case of a disease, when drug is given to the effected person it will bind with the target molecule, taking part in the formation of a disease. The drug will try to inhibit the contribution of the target molecule to stop the disease from progress. Drugs function in two ways they either start or stop the activity of target molecule (Stockwell, 2007). The target should be the main key molecule which initiates the disease by signaling or metabolic pathway. The target molecule can be a protein or DNA; it depends on the disease mechanism.

6. Molecular Docking

I downloaded pdb file of protein from protein data bank and downloaded the ligands files as sdf from the pub chem. database. Then modified the structure of ligands in discovery studio 4.1 and opened the protein in discovery studio 4.1 and remove the water molecules in discovery studio 4.1 and saved as pdb files. Then I opened protein in autodock and made a grid box and values were

```
center_x=38.78
center_y=17.896
center_z=99.74
size_x=76
size_y=80
size_z=126
```

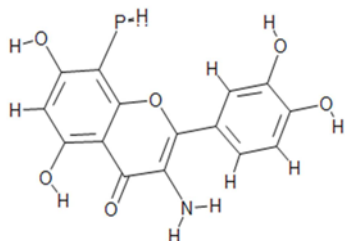
And saved as pdbqt files then opened the ligand in autodock and saved as pdbqt files. Protein and ligands opened in autodock vina and precede docking and got the results.

7. Results and Discussions

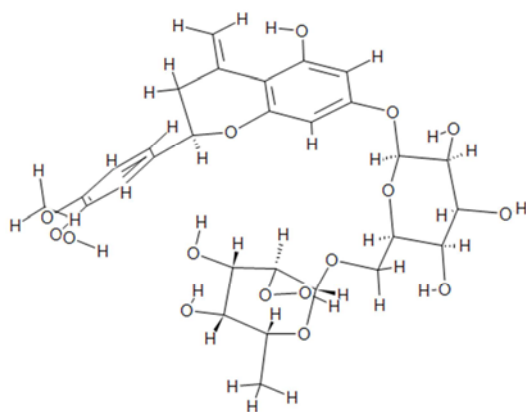
The code of target protein is 2hod. The PDB file of target protein was downloaded from NCIB. I found five ligands and modified their structures one by one. After that I started docking. The ligands chosen were apigenin, hesperidin, menisdaurin, pedunculagin, procyanidinB5. I modified them as shown in Table 1

Table 1. Modifications done to the Original Ligands.

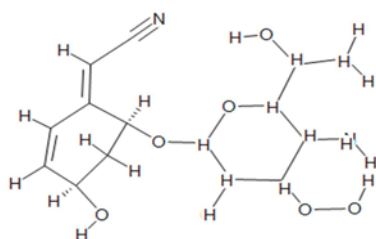
Ligand name	R1	R2	R3
Apigenin	H ₂₁ →N ₂₁	H ₂₇ →O ₂₇	H ₂₂ →P ₂₂
Hesperidin	H ₇₄ →O ₇₄	O ₁₃ →C ₁₃	H ₆₂ →O ₆₂
Menisdaurin	H ₄₁ →O ₄₁	H ₃₉ →O ₃₉	O ₂ →N ₂
Pedunculagin	O ₉ →N ₉	H ₅₇ →O ₅₇	H ₇₁ →N ₇₁
ProcyanidinB5	H ₆₈ →N ₆₈	H ₅₃ →O ₅₃	H ₆₁ →P ₆₁



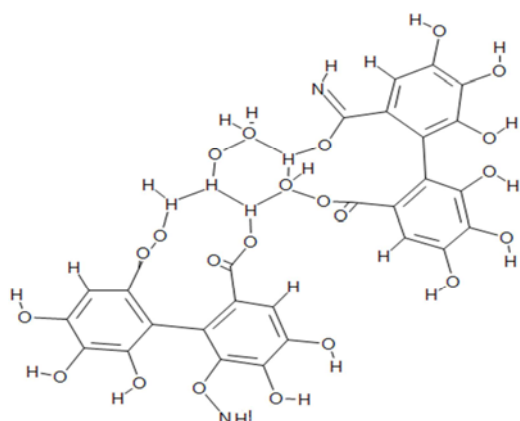
Apigenin.



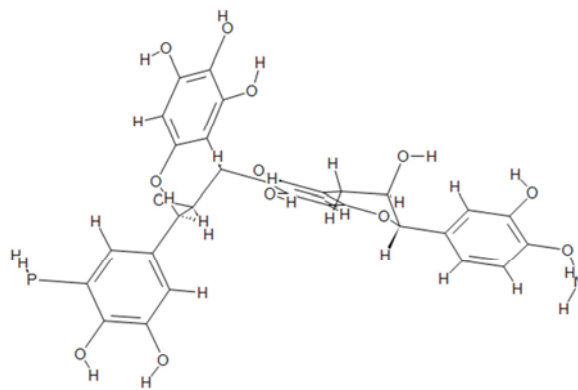
Menisdaurin.



Hesperidin.



Pedunculagin.



ProcyanidinB5.

Ligands interaction with the target protein:
1. Apigenin derivative:

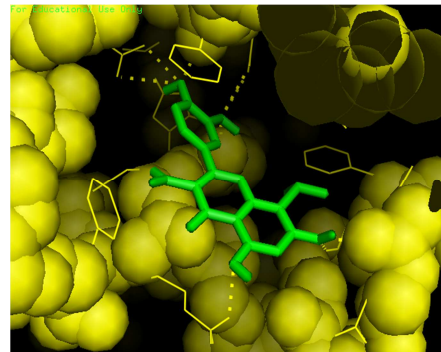
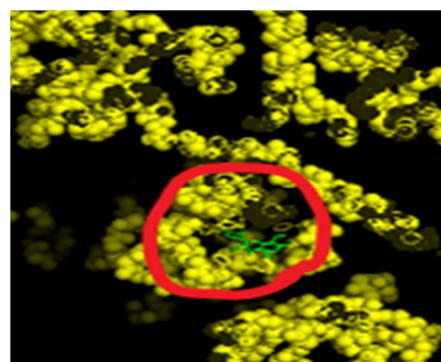
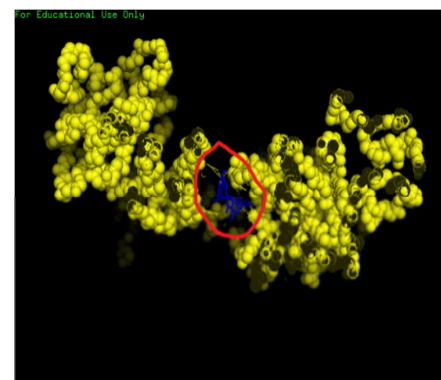


Figure 1. Predicted Bonded Interaction between Modified Apigenin with PCGF2 Protein.

2. Hesperidin derivative:



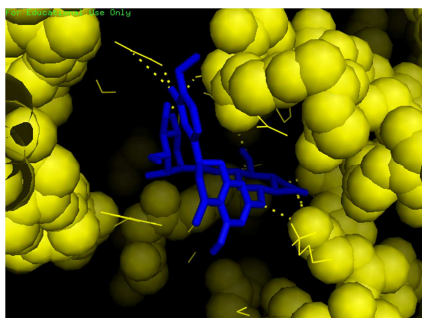


Figure 2. Predicted Bonded Interaction between Hesperidin Derivative with PCGF2 Protein.

3. Menisdaurin derivative:

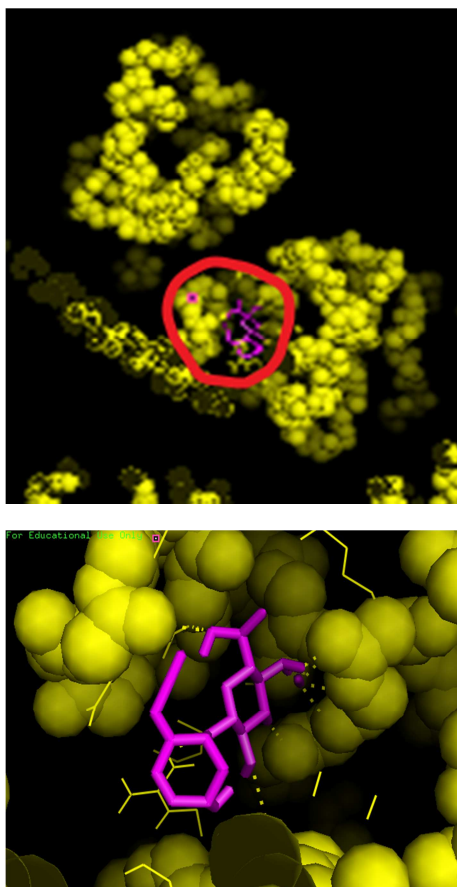


Figure 3. Predicted Bonded Interaction between Menisdaurin Derivative with PCGF2 Protein.

4. Pedunculagin derivative:

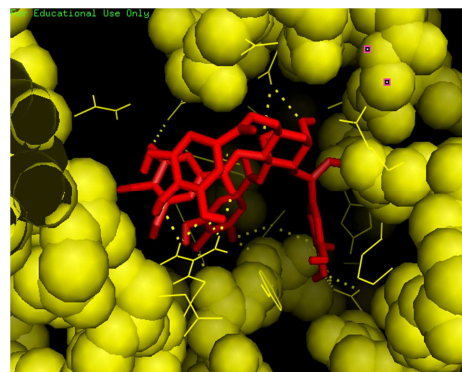
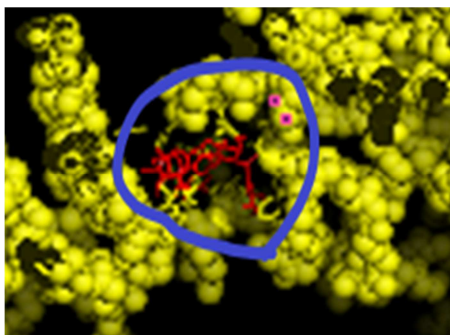


Figure 4. Predicted Bonded Interaction between Pedunculagin Derivative with PCGF2 Protein.

5. Procyanidin B5 derivative:

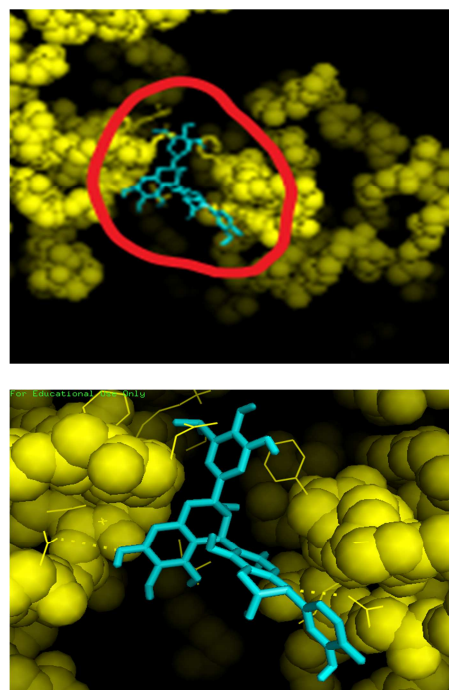


Figure 5. Predicted Bonded Interaction between Procyanidin B5 Derivative with PCGF2 Protein.

DOCKINGRESULTSOF LIGANDSWITHPROTIEN:

Table 2. Docking Energies of Different Ligands with PCGF2 Protein.

Name	Ligands	1	2	3	4	5	6	7	8
Apigenin	Orgnl	-8.3	-8.1	-8.1	-8.0	-8.0	-8.0	-7.9	-7.8
	Modif	-8.7	-8.3	-8.0	-7.8	-7.8	-7.6	-7.6	-7.6
Hesperidin	Orgnl	-8.5	-8.2	-8.2	-8.1	-8.0	-8.0	-7.7	-7.7
	Modf	-9.5	-9.3	-9.1	-8.9	-8.9	-8.7	-7.9	-7.8
Menisdaurin	Orgnl	-7.4	-7.4	-7.3	-7.1	-6.9	-6.9	-6.9	-6.9
	Modf	-8.5	-7.7	-7.7	-7.3	-7.3	-7.3	-7.3	-7.2
Pedunculagin	Orgnl	-10.6	-10.5	-10.4	-10.3	-10.2	-10.2	-9.9	-9.4
	Modf	-10.1	-10.0	-9.9	-9.8	-9.7	-9.7	-9.7	-9.6
ProcyanidinB5	Orgnl	-9.3	-9.2	-9.1	-9.0	-8.9	-8.8	-8.6	-8.6
	Modf	9.0	-8.9	-8.5	-8.5	-8.5	-8.1	-8.1	-8.1

ABMETproperties:

ADMET properties of modified ligands extracted from *Cowania mexicana* are given below in Table 3

Table 3. ADMET Properties of Modified Ligands.

Structure name	MlogP	S+logP	S+logD	Rule of 5	Ruleof5_code	MWT	M_NO	T_PSA	HBDH
Ligand 1 (mdf apigenin)	-0.235	3.018	3.018	1.000	Hb	333.239	7.000	137.150	6.000
Ligand 2 (mdf hesperidin)	-1.563	-0.212	-0.235	3.000	Hb,Mw,NO	640.599	16.000	235.680	8.000
Ligand 3 (mdf menisdaurin)	-1.595	-1.238	-1.806	1.000	Hb	342.351	9.000	158.420	6.000
Ligand 4 (mdf pedunculagin)	-5.377	-0.075	-0.796	3.000	Hb,Mw,NO	814.585	24.000	419.450	16.000
Ligand 4 (mdf procyanidin)	-1.458	2.545	2.599	3.000	Hb,Mw,NO	641.529	14.000	256.010	12.000

Table 4. Drug Scoring of Modified Ligands.

LIGANDNAME	ligand	Rmsd	Rank(score)	score
Ligand1	0	None	1	577
Ligand2	0	None	1	668
Ligand3	0	none	1	44
Ligand4	0	none	1	344
Ligand5	0	none	1	-97

8. Conclusion

Our molecular docking results show that the derivatives of the compounds we selected for this study i.e. Pedunculagin, Procyanidin 5, Hesperidin, Menisdaurin and Apigenin showed better interaction with the target protein PCGF2. These results show that these compounds can prove novel in our fight against breast cancer.

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