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

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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 mexicana (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 mexicana and its derivates 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 stormal cells (Barbarestani 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 zing finger 1
and 2 (Yin et al., 1999). Ring finger protein causes formation of multiprotein complexes and mediates interactions between different proteins (Hammamo 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).

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  | center_y | center_z |
|----------|----------|----------|
| 38.78    | 17.896   | 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 preceded 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 NCBI. I found five ligands and modified their structures one by one. After that I started docking. The ligands chosen were apigenin, hesperidin, menisdaurin, pedunculagin, procyanadinB5. I modified them as shown in Table 1.
Table 1. Modifications done to the Original Ligands.

| Ligand name   | R1        | R2        | R3        |
|---------------|-----------|-----------|-----------|
| Apigenin      | H₂₁→N₂₁  | H₂₇→O₂₇  | H₃₂→P₂₂  |
| Hesperidin    | H₁₄→O₂₄  | O₁₅→C₁₅  | H₃₂→O₂₂  |
| Menisdaurin   | H₁₄→O₁₄  | H₉₉→O₉₉  | O₂→N₂    |
| Pedunculagin  | O₈→N₉    | H₅₇→O₅₇  | H₇₁→N₇₁  |
| ProcyanidinB5 | H₆₈→N₆₈  | H₃₅→O₃₅  | H₆₃→P₆₃  |

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

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

2. Hesperidin derivative:
3. Menisdaurin derivative:

4. Pedunculagin derivative:

5. Procyanidin B5 derivative:

**Docking Results of Ligands with PCGF2 Protein:**

| Name               | Orgnl | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   |
|--------------------|-------|-----|-----|-----|-----|-----|-----|-----|-----|
| Apigenin           | Orgnl | -8.3| -8.1| -8.0| -8.0| -8.0| -7.9| -7.8|     |
|                    | Modif | -8.7| -8.3| -8.0| -7.8| -7.6| -7.6| -7.6| -7.6|
| Hesperidin         | Orgnl | -8.5| -8.2| -8.1| -8.0| -8.0| -7.7| -7.7|     |
|                    | Modif | -9.5| -9.3| -9.1| -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|
|                    | Modif | -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|
|                    | Modif | -10.1| -10.0| -9.9| -9.8| -9.7| -9.7| -9.7| -9.6|
| Procyanidin B5     | Orgnl | -9.3| -9.2| -9.1| -9.0| -8.9| -8.8| -8.6| -8.6|
|                    | Modif | 9.0 | -8.9| -8.5| -8.5| -8.5| -8.1| -8.1| -8.1|

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