6-Gingerol from Zingiberaceae as a Result of Reverse Docking for Prostate’s Cancer Potential Drug Candidate

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Abstract
Prostate cancer is a cancer that attacks the prostate gland causing the death rate which is high enough. One of the causes of prostate cancer is the androgen receptor (AR) in the gland cells that initiates the formation of excess cell proliferation, thus causing prostate cancer. AR inhibitor that is known is antiandrogen (biculatamide and enzalutamide). This study aimed to test the 6-gingerol compound of ginger as an AR inhibitor drug candidate for prostate cancer using silico method. The 3D structure of the 6-gingerol compound was taken from PubChem, the prediction of targeted protein used SwissTargetPrediction and Pharmmapper, analysis and docking 6-gingerol and antiandrogens with AR using PyRx software, visualization compounds and protein interactions using PyMOL software. Visualization results show that the interaction of 6-gingerol, biculatamide, and enzalutamide with AR have the same site. This proves that the 6-gingerol is potential as an AR inhibitor candidate.

Keywords: 6-gingerol; prostate’s cancer; reverse docking

1. Introduction
The second most common cancer diagnosed in U.S. males, after nonmelanoma skin cancer, is prostate cancer. Estimates are that in 2000, 180,400 cases of prostate cancer were diagnosed in the United States and 31,900 men died of the disease [1]. One of causing factor for prostate cancer is androgen receptor. The androgen receptor (AR) is required for prostate cancer growth in all stages, including the relapsed, androgen-independent tumors in the presence of very low levels of androgens [2]. The AR modulates the expression of genes involved in proliferation and differentiation. The AR belongs to the steroid receptor family of the nuclear receptor superfamily. This family consists of the glucocorticoid, estrogen, progestosterone and mineralocorticoid receptors [3].

Prostate tumor cells appear to have several possible mechanisms by which they could become androgen refractory. First, mutations in the AR hormone-binding domain or amplification of the AR gene could increase tumor cell sensitivity to the very low levels of androgens that are produced by the adrenal glands. Second, mutations of the AR could allow it to respond to other steroids or even to antiandrogens. Third, alterations of the interactions between the AR and some of its coactivators could allow unmutated or mutated AR to become activated by adrenal androgens, other steroids, or antiandrogens. Standard treatments relies on removing, or blocking the actions of, androgens [1].

Treatments such as androgen deprivation therapy (ADT), which typically includes suppression of testicular androgen by surgical castration or treatment with analogues of luteinizing hormone releasing hormone, are effective at slowing disease progression. In advanced disease, however, the cancer progresses despite low levels of circulating androgens that result from ADT [4]. The novel rationally designed AR signaling inhibitor (ARSI) enzalutamide (formerly MDV3100) is a phenylthiohydantoin derivative with kia sulfonamide side chain [5]. Enzalutamide has not only been shown to potently inhibit the binding of androgens to the AR, but also inhibit nuclear translocation and subsequent binding of the AR-ligand complex to DNA, thereby inhibiting transcription of AR target genes. In contrast to antiandrogens (biculatamide and enzalutamide) does not induce agonistic effects on AR signaling in cells over-expressing wild type AR [6]. 6-gingerol compounds from Zingiberaceae alleged can be used as antiandrogens for prostate cancer treatment.

Ginger is a natural dietary ingredient with antioxidant, anti-inflammatory, and anticarcinogenic properties [7]. Ginger contains several pungent constituents such as gingerols, shogaols, paradoxols, and gingerdiols [8]. Gingerols were identified as the major active components in fresh ginger rhizome with 6-gingerol being the most abundant constituent [9]. 6-gingerol inhibited cell proliferation, induced apoptosis, and G1 cell-cycle arrest in human colorectal cancer cells [10]. As a drug candidate, various tests related to the degree of effectiveness are needed to those compounds [11].

One of the parameters used in drug design is whether the drug candidate compound meets the Lipinski rule of five or not [12]. Lipinski’s rule of five is a rule of thumb formulated by Christopher A. Lipinski in 1997, to evaluate the “drug-likeness” of a chemical compound, and to allow a quick, reasonably-accurate determination as to whether or not a molecule with interesting biactive is also likely to be an orally available drug in humans [13]. Simply, it defined several rules for identifying compounds with possible poor absorption and permeability [14]. This study aim to show 6-gingerol from Zingiberaceae as drug candidate for treatment in human prostat cancer. The result of this study are expected to replace antiandrogens (biculatamide and enzalutamide) with natural product from Zingiberaceae.
2. Material and Methods

2.1. Ligand preparation

2.2. Target selection
Input 6-gingerol’s SMILES to Pharmmapper [16] and SwissTargetPrediction [17]. PharmMapper server is web server designed to identify potential target candidates for the given small molecules (drugs, natural products or other newly discovered compounds with unidentified binding targets) using pharmacophore mapping approach [18]. While SwissTargetPrediction is a web server to accurately predict the targets of bioactive molecules based on a combination of 2D and 3D similarity measures with known ligands [19].

2.3. Molecular docking
Molecular docking 6-gingerol, target protein, and inhibitors of target protein used PyRx 0.8 software.

2.4. Visualization of molecule and small molecule interaction
The interactions 6-gingerol, target protein, and inhibitors of target protein visualized and analyzed using LigPlus and PyMol.

2.5. Lipinski’s rule of five analysis
The drug compound tested using Molinspiration webserver to test whether the pipelines meet the criteria of Lipinski’s rule of five or not [20].

3. Results and Discussion
The result of target selection using Pharmmapper and SwissTargetPrediction database shows that 6-gingerol compound interact with AR in human body. The known inhibitors of androgen receptor are enzalutamide and bicalutamide. The visualization result using PyMol software shows 6-gingerol, bicalutamide and enzalutamide have the same interaction. That interaction shows that 6-gingerol and enzalutamide interact with AR in the same site. The interaction of AR inhibitors is shown in Figure 2.

Figure 1. Interaction between protein target (androgen receptor) and inhibitors (6-gingerol, bicalutamide and enzalutamide) show that inhibitors bind the protein target at the same site. Information: androgen receptor (green), bicalutamide (yellow), enzalutamide (red), and 6-gingerol (blue).

Protein-ligand interaction show in 2D visualization using LigPlus software. The result shows that the protein-ligand interaction between bicalutamide with AR as shown (Figure 3a) involves some amino acid residues through hydrophobic bonds, such as Glu 678, Glu 681, Pro 682, Val 685, Gly 683 and with Arg 752 through both hydrophobic interaction and hydrogen bond. On the other inhibitors, protein-ligand interaction between enzalutamide and AR (Figure 3b) also involved some amino acid residues with hydrophobic interaction, such as Pro 801, Gln 802, Phe 804, Leu 805, Trp 751, Asn 756, and Thr 755. Interaction between 6-gingerol and AR as shown (Figure 3c) some amino acid residues, such as Gln 711, Trp 718, Pro 682, Leu 744, Gly 683, Lys 808, Val 715, Ala 748, Glu 681, Trp 751, Asn 756, and Thr 755. Enzalutamide and 6-gingerol have interaction with Arg 752 through both hydrophobic interaction and hydrogen bond too.
AR signaling has a major role in advanced prostate cancer, which is hormone refractory or androgen independent [21]. At this stage, even though the levels of circulating androgens are low, through various mechanisms, such as amplification of the AR gene and upregulation of AR. The treatment for prostate cancer are using inhibitor to block protein-ligand binding interactions of AR. The result from reverse docking of 6-gingerol and antiandrogens (bicalutamide and enzalutamide) with protein target AR, show both of inhibitors are block androgen receptor in same site. The visualization from LigPlus shows that there are three similar amino acids which is boundto 6-gingerol and bicalutamide. Those amino acids are Glu 681, Arg 752, and Gly 683. Interactions between 6-gingerol with other antiandrogen enzalutamide also has similar amino acids bound, there are Arg 752, Trp 751, Asn 756, and Thr 755. Those amino acids are actively involved in the intermolecular interaction of protein-ligand complex at AR.

Two or more ligands that bind on the same site of protein domain have similar biochemical mechanism and being involved in relevant biological pathway [22]. It means that 6-gingerol has a possibility to have similar inhibitory activity with bicalutamide and enzalutamide. It shows that the 6-gingerol compound from Zingiberaceae can be used as substitute for enzalutamide compound which has role as antiandrogens. Related to the bioavailibility and Lipinski’s rule, Kujawski, et al. explained the optimal lipophilicity range along with low molar mass and low polar surface area is the driving force that leads to good absorption of chemicals in the intestine by passive diffusion [23]. The rule of 5 is now implemented in our registration system for new compounds synthesized in our medicinal chemistry laboratories and the calculation program runs automatically as the chemist registers a new compound. If two parameters are out of range, a poor absorption or permeability is possible alert appears on the registration screen (lipinski). According to Table 1, 6-gingerol have good bioavailibilty based on the lipinski's rule of five analysis. It means that 6-gingerol can be used as a powerful drug candidate as a replacement of bicalutamide and enzalutamide as antiandrogens. Thus, based on this research, this compound could be the most potential drug candidate for the treatment of prostate cancer.

4. Conclusion
6-gingerol drug candidate can be use as replacement antiandrogens (bicalutamide and enzalutamide) as prostate cancer treatment

References


[16] Pharmapper. (http://59.78.96.61/pharmmapper/)

[17] SwissTargetPrediction. (http://www.swisstargetprediction.ch)


