ORIGINAL ARTICLE

The Potential of Cammelia sinensis (Tea Leaves) Active Compound as Alternative Therapy on castrate-resistant prostate cancer (CRPC) with Androgen Receptor Inhibition: In Silico Study

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ABSTRACT

Introduction: Prostate cancer is a leading global cause of increased mortality and morbidity in men which can be complicated by castrate-resistant prostate cancer (CRPC). Pharmacological therapy by inhibiting the androgen receptor (AR) can inhibit prostate cancer progression. Tea leaves (Camellia sinensis) are believed to inhibit the prostate cancer progression but the mechanism is still unknown. Therefore, research on the mechanism by in silico study is needed with the AR as target protein.
Methods: The effectivity of tea leaves' active compound to inhibit androgen receptor was evaluated by docking server with abiraterone acetate as a control. The tea leaves' active compounds consist of catechin, epicatechin, epigallocatechin gallate, epigallocatechin, gallate epicatechin, gallocatechin gallate, and gallocatechin
Results: The result showed that epicatechin, epigallocatechin, and gallocatechin have lower free binding energy (ΔG) and high amino acid residue similarity on AR compared with abiraterone acetate. But, it has lower surface interaction compared with abiraterone acetate.
Conclusion: Epicatechin, epigallocatechin, and gallocatechin are predicted to have potential as alternative therapy in CRPC with AR Inhibition.

Introduction

Prostate cancer is a leading global cause of increased mortality and morbidity of men. The incidence of prostate cancer is estimated at 233,000 with 29,480 deaths in 2014. In America, cancer is the second leading cause of death due to cancer in men.[1] Based on data from GLOBACAN 2012, prostate cancer is the third most common cause of cancer in Indonesia. The incidence of prostate cancer increases with age and the improving detection of prostate cancer. The incidence of prostate cancer in Indonesia increased from 10.6 per 100,000 men in 2008 to 14.8 per 100,000 in 2012.[2] One of the complications of prostate cancer is castration resistant prostate cancer (CRPC). CRPC is a castration failure that prevents an increase in androgen hormones, which worsens the prostate cancer.[3–5]

The main treatment for CRPC is to provide androgen deprivation therapy (ADT), which comprises docetaxel, cabazitaxel, and abiraterone acetate.[6] ADT works by inhibiting the androgen receptor (AR) thus inhibiting the androgen hormone with AR.[7] This inhibition decreases the proliferative effect in prostate cancer.[8,9] However, administration of ADT may cause resistance so that a second line of ADT is needed which causes subsequent resistance.[10–13] Therefore, it is important to find alternative therapies for prostate cancer.[14]

Green tea (Camellia sinensis) is a herb that is easy to grow, cultivate, and it is often consumed by some of the community. Green tea is known to have antioxidant, apoptotic, and inhibition of growth factor signaling effects in vitro on prostate cancer cells.[15] Research by Siddiqui et al. showed that the green tea compound epigallocatechin-3-gallate could inhibit AR in silico and inhibit cell lines from prostate cancer.[16,17] In this study, only one extracted compound from green tea was tested and it did not use ADT control for comparison with AR.

Based on the review above, further in silico research is needed using several green compounds and using

ADT control.

Methods

Study Design

The design of this study used in silico method with a tea leaf compound (*Camellia sinensis*) which consists of catechin, epicatechin, epigallocatechin gallate, epigallocatechin, gallate epicatechin, gallocatechin gallate, and gallocatechin to androgen receptor as a target proteins. This research was conducted August to September 2021

Protein and Ligan Preparation

The structure of the tea leaf active compound downloaded from https://pubchem.ncbi.nlm.nih.gov/ by using code was: catechin (ID: 9064), epicatechin (ID: 72276), epigallocatechin gallate (ID: 65064), epigallocatechin (ID: 72277), gallate epicatechin (ID: 107905), gallocatechin gallate (ID: 199472), and gallocatechin (ID: 65084). Control ligand used was abiraterone acetate (ID: 9821849). Target protein androgen receptor (AR) was found using Protein Data Bank with IE3G code. The hardware used was Intel® Pentium® Core i5 @1.86Ghz, RAM 4 GB, Windows 10 64-bit Operating System and connected to the internet. The downloaded ligand compound from PubChem was then tested to molecular docking for the target protein. This test used www.dockingserver.com

Data Analysis Techniques

In silico test results were observed with free bond energy (ΔG), interaction between molecules, surface interactions between ligands and target proteins

Results

The results of the green tea molecular docking test are listed in Table 1. Based on these, it shows that the free energy resulting from the interaction of these compounds from smallest to largest is catechin, epicatechin, epigallocatechin, gallocatechin, gallate epicatechin, epigallocatechin gallate, and gallocatechin gallate. The active compounds in tea leaves that have less energy than the control are catechins, epicatechins, epigallocatechins, gallocatechins, and gallate epicatechins.

The interaction between control ligand molecules with target protein produces hydrogen bonds to the amino acid residues ASN705, ARG752, and THR877. All active compounds have hydrogen bonds in common with control ligands. Amino acids with the smallest hydrogen which bond similarly are catechins and gallate epicathecin (Table 1).

Figure 1 shows that the size of the chemical structure from the largest to the smallest is abiraterone acetate > epigallocatechin gallate > catechin. The surface interaction

Table 1. Green Tea Active Compound Molecular Docking Results

Target Protein	Ligand	Free Energy (kcal/mol)	Intermolecular Interaction (Hydrogen Bonding)	Surface Interaction (A°)
Androgen Receptor	Abiraterone acetate (C)	+2.14	ASN705, ARG752, THR877	681.11
	Catechin	-7.70	GLN711, ARG752*	495.39
	Epicatechin	-7,56	ARG752*,THR877*	494.67
	Epigallocatechin gallate	+3,45	GLN711, ARG752*, THR877*	640.51
	Epigallocatechin	-7,56	ARG752*,THR877*	494.59
	Gallate epicatechin	+0,04	THR877*	598.26
	Gallocatechin gallate	+7,35	ASN705*, THR877*	605.33
	Gallocatechin	-7,22	ARG752*, THR877*	505.08

Note: C, Control; IG, Hydrogen Bonding; * , hydrogen bond similar with control

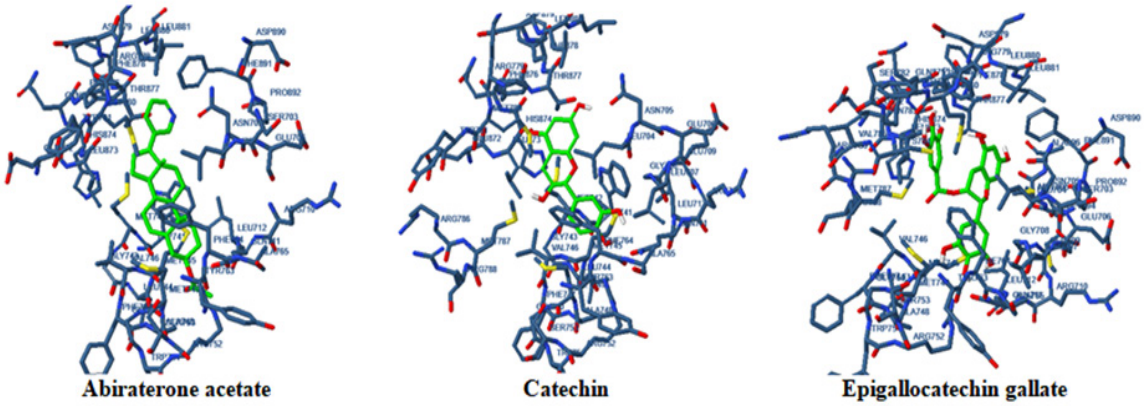

Figure 1. The interaction of ligand binding and target protein

of active compounds of tea leaves has a lower value than the control. The order of surface interactions of active compounds from smallest to largest is epigallocatechin, epicatechin, catechin, gallocatechin, gallate epicatechin, gallocatechin gallate, and epigallocatechin gallate.

Discussion

The lower free binding energies than control were catechin, epicatechin, epigallocatechin, gallocatechin, and gallate epicatechin (Table 1). The free bond energy is the energy required for the interaction between the ligand and the receptor. This energy also figures out the spontaneity of the ligand binding to the receptor. The lower the free bond energy, the more spontaneous the bond will react. In addition, the low free energy also indicates that the bond is strong and causing biological activity.[18]

Interaction between molecules is the interaction which occurs between the active site of the receptor and the ligand compound. In this study, the formed active sites from control and AR ligands were found in amino acid residues ASN705, ARG752, and THR877. In the amino acid residues, hydrogen bonds are formed between hydrogen ions with elements charged electronegatively. This increase of hydrogen bonding strengthens the bond between the ligand and the receptor. In this study, the active compounds in tea leaves that had the same amino acid residue as AR and lower free energy than the control were epicatechin, epigallocatechin, and gallocatechin (Table 1). In addition, there are other compounds that have lower free bond energies than control and have different amino acid residues, which are catechins. The different amino acid residues indicate that these compounds can bind to the other side of the AR so that it has the potential to inhibit AR under mutational conditions.[19] This is caused by protein receptors that undergo mutations so that hydrogen bonds change.[20]

Surface interactions can also affect the affinity between the ligand and the receptor. High surface interactions provide a high chance to bind to receptors.21 In this study, the whole active compounds in tea leaves had a smaller surface interaction value than the control. Surface interactions can be affected by the size of the ligand molecule.[21] The surface interaction value was thought to be caused by the smaller size of the tea leaf active compound compared to the control (Figure 1).

In this study, AR was used as a target. AR is part of a super family of steroid hormones that has four functional domains, which are ligand-binding domain (LBD), DNA-binding domain (DBD), hinge region and N-terminal domain (NTD).[5] When AR gets ligand binding with androgen hormones, transcription and several growth signaling pathways occur to increase the cell proliferation and anti-apoptotic effects.[5,22] Therefore, alternative therapy is needed to inhibit the interaction between androgen hormones with AR.[23,24]

Based on the results of molecular docking, it estimated that epicatechin, epigallocatechin, and gallocatechin compounds have a higher affinity than controls in inhibiting AR.

Conclusion

There were only three active compounds of tea leaves, epicatechin, epigallocatechin, and gallocatechin, having the potential to work as an alternative to ADT by inhibiting AR, because they had the same amino acid residue as AR and lower free energy than the control. The other active compound didn't have the potential to inhibit AR. Further research is needed such as in vitro and in vivo to confirm that epicatechin, epigallocatechin, and gallocatechin compounds are able to work as an alternative to ADT by inhibiting AR

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Conflict of Interest

The Authors declares that there is no conflict of interest.

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