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J.Biomed.Transl.Res
ISSN: 2503-2178

JOURNAL OF BIOMEDICINE AND TRANSLATIONAL RESEARCH

Available online at JBTR website: https://jbtr.fk.undip.ac.id

Original Research Article

Revealing the Potency of Camelia sinensis and Serenoa repens as Purinoreceptor Inhibitor for Benign Prostatic Hyperplasia Treatment Through in Silico Study

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Article Info
History
Received: 06 Dec 2023
Accepted: 13 Aug 2024
Available: 30 Aug 2024

Abstract

Background: Benign prostatic hyperplasia (BPH) is the most common prostate disease in elderly men that leads to a significant deterioration in patients' quality of life (QoL). Pharmacological therapy of 5-alpha reductase inhibitor and alpha adrenoreceptors blocker often causes several side effects that decrease the QoL, so it is necessary to develop a new treatment for BPH. Purinoreceptor is a novel receptor that can inhibit electrically evoked nerve-mediated contractions in the prostate. Tea leaves (*Camellia sinensis*) and Saw palmetto (*Serenoa repens*) are herbs that have potential as alternative therapies for BPH

Objective: to reveal the potency of *Camelia sinensis* and *Serenoa repens* as purinoreceptor inhibitor for benign prostatic hyperplasia treatment through in silico study

Methods: This study using in silico method. Structures of active compounds were extracted from PubChem and protein from Protein Data Bank (PBD). The active compounds *Camellia sinensis* and *Serenoa repens* to the target protein *purinoreceptors, 5-alpha-reductase,* and *alpha adrenoreceptors* was evaluated *in silico* using a docking server with Finasteride dan Tamsolusin as a control. Molecular docking method using docking server application.

Results: Epigallocatechin gallate only compound that has potency in blocking purinoceptors and 5-alpha-reductase with free energy binding -6.81 kcal/mol and -6.79 kcal/mol. Capric acid, Caprylic acid, Lauric acid, Linoleic acid, and Myristic acid have the potential to bind to alpha adrenoreceptor ligands with free energy binding-4.37 kcal/mol, -4.04 kcal/mol, -3.75 kcal/mol, -3.08 kcal/mol, and -3.24 kcal/mol.

Conclusion: In silico study showed that *Camellia sinensis* have potential and effects as alternative therapies in benign prostatic hyperplasia on the target protein purinoreceptors, 5-alpha-reductase, and alpha adrenoreceptors. But, *Serenoa repens* have potential only through alpha adrenoreceptors. This study offers a potential alternative for BPH treatment using natural components. This is significant given the need for safer treatment options with fewer side effects compared to conventional therapies.

Keywords: *Camellia sinensis; Serenoa repens; Benign prostatic hyperplasia; In silico; Purinoreceptor*
Permalink/ DOI: https://doi.org/10.14710/jbtr.v10i2.21211

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a non-malignancy growth of prostate tissue. BPH are common cause lower urinary tract symptom (LUTS) in elderly man. BPH is increases at the age of 90 years old with prevalence 8%-60%.[1]

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BPH can causes obstruction by increases compression due to increases prostate volume and smooth muscle[2]. Manifestation of hyperplasia prostate are urgency, nocturia, hesitancy, streaming, straining, and prolong micturition[3]. Common complications of BPH are urinary tract infection, hydronephrosis, nephrolithiasis.[2]

Early treatment of patient with BPH is modification of life style or pharmacology therapy. Pharmacology therapy that can use in with BPH is 5-alpha- reductase inhibitor such as Finasteride and alpha blocker such as Tamsolusin[4]. Mechanism action of 5-alpha-inhibit growth effect androgen in testosterone with reduction of testosterone conversion to dihydrotestosterone. Alpha-blocker works by relaxing smooth muscle of prostate and bladder neck with inhibit sympathetic nerve[3]. This two class therapy of BPH have any adverse effect such as impotence, decreased libido, and ejaculation dysfunction and hypotension.[3] So another treatment with minimal adverse effect is needed in BPH.

In early decade, another research showed that there was a P2X-purinoceptor in smooth muscle of prostate[5]. Purinoreceptor are ATP-gated and acetylcholine canal that location in musculus detrusor[6]. Blockade in this receptor can inhibit parasympathetic innervation that can make relaxation of detrusor[6]. This receptor is not found in blood vessel so it does not cause vasodilatation of blood vessels[6]. So, we need to evaluate the potency of P2X-purinoreceptor as target protein on BPH treatment. Indonesia is a country with more than 6000 herb that can use as traditional medication[7]. Tea (*Camelia sinensis*) is one of the Indonesian herb that has potential as BPH treatment[8] and prostate cancer[9]. Tea contains compounds epigallocatechin gallate, gallocatechin gallate, gallocatechin, catechin, epicatechin, gallate epicatechin dan epigallocatechin[10]. In addition saw palmetto (*Serenoa* repens) has potential as BPH treatment.[11] This herb contains *Lauric acid* (30,2%), *Myristic acid* (12,0%), *Oleic acid* (28,5%), *Palmitic acid* (9,5%), *Linoleic acid* (4,6%) dan *Capric acid* (2,5%).[10] However mechanism action is still unknown, further research is needed [11]. Based on explanation above, further research is needed to know the potential of Tea and Saw palmetto active compounds as alternative treatment on BPH through in silico study. In silico studies are essential for researching the potential of tea and saw palmetto compounds as BPH treatments due to their cost-effectiveness, time efficiency, and ability to screen large compound libraries quickly. Additionally, they facilitate personalized medicine by modelling compound effects on different genetic profiles, making them a crucial preliminary step before costly and time-consuming in vitro and in vivo studies.

MATERIALS AND METHODS

This study use in-silico method by analyzing the interaction of *Camellia sinensis* and *Serenoa repens* which contain capric acid, caprylic acid, catechin, epicatechin, epigallocatechin gallate, epigallocatechin, finasteride (K), gallate epicatechin, gallocatechin gallate, gallocatechin, lauric acid, myristic acid, oleic acid, linoleic acid and palmitic acid to three target proteins which are 5-alpha-reductase, purinoreceptor, dan alpha adrenoreceptor.

Material and tools

The structure of the active compounds *Camellia sinensis* and *Serenoa repens* which consist of Capric acid (ID:2969), Caprylic acid (ID:379), Catechin (ID:9064), Epicatechin (ID:72276), Epigallocatechin gallate (ID:65064), Epigallocatechin (ID:72277), Gallate epicatechin (107906), Gallocatechin gallate (ID:199472), Gallocatechin (ID:65084), Lauric acid (ID:3893), Myristic acid (ID:11005), Oleic acid (ID:445639), Linoleic acid (ID: 5280450) dan Palmitic acid (ID:985) are gained form Pubchem.com. Ligands for control using Finasteride (ID:57363) and tamsulosin (ID:121829) gained from www.pubchem.com. This research using target protein purinoreceptor (ID:5SVQ), and alpha adrenoreceptor (ID: P35368) gained from Protein Data Bank. Target protein of 5-alpha-reductase gained from NCBI GenBank with (ID AAC26863) and converted from FASTA into PDB format using Swiss-Model website (https://swissmodel.expasy.org/). Using hardware with specification RAM 4096 MB, *Intel ® core ™* I7, CPU @2.60 GHz, system operation with *Microsoft Windows 10 Pro 64-BIT*, internet connection and *software* based on *web autodock 4.0* at *docking* server (http://www.dockingserver.com).

In Silico test of *Camelia sinensis* and *Serenoa repens* Active Compound to 5-alpha-reductase, purinoreceptor, and alpha adrenoreceptor.

The ligand compounds were downloaded in Pubchem than continue to molecular docking test by using a docking server. The docking server accessed at (http://www.dockingserver.com).

Data Analysis Technique

In this study, Lipinski's Rule of Five was employed to assess the drug-likeness of plant compounds intended for medicinal use. Ligand pharmacological testing based on Lipinski's 5 rules (RO5) is carried out to analyze the potential of a chemical compound based on pharmacological and biological activity as an oral drug for humans. Lipinski's Rule of Five accessed from http://targetnet.scbdd.com/calcnet/calc_rule_text/ . Additionally, ADMET Rule Five data were analyzed to evaluate the compounds' absorption, distribution, metabolism, excretion, and toxicity properties. These methodologies were utilized to determine the suitability of plant compounds as potential medicines and to assess their potential toxicity profiles, which were accessed from https://biosig.lab.uq.edu.au/pkcsm/prediction. In silico test were observed with parameters of free binding energy, inhibition constant, surface interaction and amino acid residues between ligand and target protein.

RESULTS

The result of Lipski Rule of Five showed on table 1. The table evaluates various active compounds according to Lipinski's Rule of Five, which predicts the drug-likeness of a molecule based on its pharmacokinetic properties. The parameters include Topological Polar Surface Area (TPSA), Molecular Weight (MW), number of Hydrogen Bond Donors, and number of Hydrogen Bond Acceptors (HBA).

Table 1. Lipinski's Rule of Five

Active Compound	TPSA	MW	Molecular Weight	Hydrogen Bond Donor	HBA	Lipinski Rule of Five (%)
Capric acid	37.3	51.9558	172.2646	1.0	2.0	100
Caprylic acid	37.3	42.3418	144.21144	1.0	2.0	100
Catechin	110.38	74.3338	290.26806	5.0	8.0	75
Epicatechin	110.38	74.3338	290.26806	5.0	8.0	75
Epigallocatechin gallate	97.37	112.0645	458.37172	8.0	13.0	50
Epigallocatechin	130.61	76.3568	306.26746	6.0	9.0	75
Gallate epicatechin	177.14	110.0415	442.37232	7.0	12.0	50
Gallocatechin gallate	197.37	112.0645	458.37172	8.0	13.0	50
Gallocatechin	130.61	76.3568	306.26746	6.0	9.0	75
Lauric acid	37.3	61.5698	200.31776	1.0	2.0	100
Myristic acid	37.3	71.1838	228.37092	1.0	2.0	100
Oleic acid	37.3	89.9378	282.46136	1.0	2.0	75
Linoleic acid	37.3	89.4638	280.44548	1.0	2.0	75
Palmitic acid	37.3	80.7978	256.42408	1.0	2.0	75

TPSA, Topological Polar Surface Area; MW, Molecular Weight; HBA, Hydrogen Bond Acceptor.

Table 2. Pharmacokinetic Characteristics

Active Compound	Absorbtion	Distribution	Metabolism				Excretion	Toxicity
	Intestinal Absorbtion (% Absorbed)	BBB Permiability (log BB)	CYP2D6 (S/I)	CYP3A4 (S/I)	CYP1A2 (I)	CYP2C9 (I)	Total Clearance (log ml/min/kg)	Hepatotoxicity
Capric acid	94.06	0.142	N/N	N/N	N	N	1.552	N
Caprylic acid	94.75	0.225	N/N	N/N	N	N	1.48	N
Catechin	68.82	-1.054	N/N	N/N	N	N	0.183	N
Epicatechin	68.82	68.820	N/N	N/N	N	N	0.183	N
Epigallocatechin gallate	47.39	-2.184	N/N	N/N	N	N	0.292	N
Epigallocatechin	54.12	-1.377	N/N	N/N	N	N	0.328	N
Gallate epicatechin	62.09	-1.847	N/N	N/N	N	N	-0.169	N
Gallocatechin gallate	47.39	47.39	N/N	N/N	N	N	0.292	N
Gallocatechin	54.12	-1.377	N/N	N/N	N	N	0.328	N
Lauric acid	93.37	0.057	N/N	N/N	N	N	1.623	N
Myristic acid	92.69	-0.027	N/N	N/N	N	N	1.693	N
Oleic acid	91.82	-0.168	N/N	Y/N	Y	N	1.884	N
Linoleic acid	92.32	-0.142	N/N	Y/N	Y	N	1.936	Y
Palmitic acid	92.00	-0.111	N/N	Y/N	N	N	1.763	N

S, substrate; I, inhibitor; Y, Yes; N, No

The percentage compliance with Lipinski's Rule of Five is also listed. Compounds like Capric acid, Caprylic acid, and Lauric acid show 100% compliance, indicating high potential as drugs due to favourable properties such as lower molecular weight, appropriate hydrogen bonding capacity, and suitable lipophilicity. Conversely, compounds like Gallocatechin gallate and Gallic acid have only 50% compliance, suggesting potential issues with bioavailability and absorption due to their higher molecular weight and excessive hydrogen bonding characteristics.

The result of pharmacokinetics characteristics showed on table 2. The table presents the pharmacokinetic characteristics of various active compounds, focusing on absorption, distribution, metabolism, excretion, and toxicity. Intestinal absorption percentages range from 47.39% to 94.75%. Blood-Brain Barrier (BBB) permeability values (log BB) vary from -2.184 to 0.225. Metabolic interactions are noted with several CYP enzymes, where most compounds do not act as substrates or inhibitors (N/N). Total clearance rates, measured in log ml/min/kg, span from -0.169 to 1.936. Only Gallic acid showed hepatotoxicity. Based on these factors, compounds such as Capric acid and Lauric acid appear to be the safest, while Gallic acid is the least safe due to its hepatotoxicity.

The result of molecular docking showed on table 3. The result of molecular docking between 5-alpha-reductase ligand and epigallocatechin gallate compound has a lower free energy than the control tamsulosin while other compounds have a greater free binding energy than the control. *Purinoreceptor* ligand showed that epigallocatechin gallate, gallate epicatechin, and gallocatechin gallate, has lower free binding energy than control finasteride.

Table 3. Result of Molecular Docking

Ligand	Active Compound	Free Energy Binding	Inhibition constant	Surface Interaction	Molecule Interaction	
					Hydrogen Bond	Hydrophobic bond
5-alpha-reductase	Capric acid	-2.50 kcal/mol	14.60 mM	405.45	-	LEU88 MET90 PHE91 HIS94
	Caprylic acid	-2.44 kcal/mol	16.17 mM	354.927	-	LEU87 LEU88 MET90 PHE91 HIS94
	Catechin	-4.22 kcal/mol	808.60 uM	439.409	SER63 TYR95	PRO62
	Epicatechin	-4.84 kcal/mol	282.64 uM	447.609	-	TRP56
	Epigallocatechin gallate	-6.79 kcal/mol	10.48 uM	710.29	-	LEU16 LEU66 PRO67
	Epigallocatechin	-4.86 kcal/mol	276.01 uM	450.051	SER63 PRO62	PRO62
	Gallate epicatechin	-6.54 kcal/mol	16.13 uM	581.701	SER63	GLN20 GLU60 TYR95
	Gallocatechin gallate	-6.17 kcal/mol	30.03 uM	600.881	SER63	SER63 PHE91
	Gallocatechin	-4.25 kcal/mol	761.31 uM	491.999	-	LEU66 PRO67
	Lauric acid	-2.77 kcal/mol	9.35 mM	449.793	-	LEU87 MET90 PHE91 HIS94 TYR95
	Myristic acid	-2.83 kcal/mol	8.42 mM	515.864	-	PRO62 LEU66 PRO67 PHE91 TYR95
	Oleic acid	-3.09 kcal/mol	5.42 mM	603.891	-	PRO67 LEU87 LEU88 PHE91 HIS94 TYR95
	Linoleic acid	-2.98 kcal/mol	6.59 mM	614.199	-	PHE91 LEU66 LEU16 PRO67 LEU88
	Palmitic acid	-2.01 kcal/mol	33.40	603.467	-	PHE91 LEU16 LEU66 PRO67 LEU88
	Finasteride (C)	-6.56 kcal/mol	15.49 uM	527.241	SER63	PRO62 LEU66 PRO67 LEU88 PHE91

Table 3. Cont.

Ligand	Active Compound	Free Energy Binding	Inhibition constant	Surface Interaction	Molecule Interaction	
					Hydrogen Bond	Hydrophobic bond
Purinoreceptor	Capric acid	-3.03 kcal/mol	6.00 mM	451.101	-	PHE171
	Caprylic acid	-2.93 kcal/mol	7.08 mM	398.097	-	PHE171
	Catechin	-4.48 kcal/mol	516.25 uM	444.259	-	MET166
	Epicatechin	-4.81 kcal/mol	295.77 uM	456.051	-	MET166
	Epicatechin	-4.86 kcal/mol	275.42 uM	453.106	-	MET166
	Epigallocatechin gallate	-6.81 kcal/mol	10.23 uM	483.764	-	MET166
	Epigallocatechin	-4.85 kcal/mol	276.55 uM	446.898	-	MET166
	Gallate epicatechin	-6.21 kcal/mol	28.07 uM	453.048	-	MET166
	Gallocatechin gallate	-5.56 kcal/mol	83.68 uM	560.567	-	
	Gallocatechin	-4.29 kcal/mol	720.41 uM	461.379	-	
	Lauric acid	-3.00 kcal/mol	6.34 mM	497.382	-	LEU69 PHE171
	Linoleic acid	-3.68 kcal/mol	2.00 mM	518.236	ARG204	PHE171
	Myristic acid	-3.05 kcal/mol	5.77 mM	465.91	-	PHE171
	Oleic acid	-3.25 kcal/mol	4.12 mM	592.546	ARG204	LEU69 VAL74 PHE171
	Palmitic acid	-3.32 kcal/mol	3.66 mM	568.769	-	VAL74 PHE171
	Tamsolusin (C)	-7.19 kcal/mol	5.39 uM	559.081	MET166 GLU169 ASN170	MET166 PHE229
	Finasteride (C)	-5.45 kcal/mol	101.23 uM	566.818	VAL309	LEU308 LEU265 ILE56
alpha adrenoceptor	Capric acid	-4.37 kcal/mol	621.98 uM	385.899	-	LEU75 CYS110 ILE114 LEU117 VAL277 PHE281 TRP285
	Caprylic acid	-4.04 kcal/mol	1.10 mM	345.563	-	LEU68 ILE114 LEU117 VAL277 PHE281 TRP285
	Lauric acid	-3.75 kcal/mol	1.78 mM	423.903	SER319	LEU68 LEU75 ILE114 LEU117 VAL277 PHE281 TRP285

Table 3. Cont.

Ligand	Active Compound	Free Energy Binding	Inhibition constant	Surface Interaction	Molecule Interaction	
					Hydrogen Bond	Hydrophobic bond
alpha adrenoceptor	Linoleic acid	-3.08 kcal/mol	5.51 mM	622.075	-	ILE276 CYS280 LEU283 CYS284 ILE321 ILE324 ILE325 CYS328
	Myristic acid	-3.24 kcal/mol	4.25 mM	525.535	-	ILE276 CYS280 ILE321 ILE324 ILE325 CYS328
	Catechin	+24.13 kcal/mol		498.394	SER113 TRY326 ASN322	LEU75 LEU117 LEU68 VAL277
	Epicatechin	+20.08 kcal/mol		495.015	TRY326 CYS110 ASN322	PHE281 LEU117 ILE114 VAL277 LEU68
	Epigallocatechin gallate	+122.24 kcal/mol		598.386	TRP285 CYS110 TYR326 SER113	SER319 ILE65 ILE120 ALA71 LEU274
	Epigallocatechin	+19.98 kcal/mol		494.835	CYS110 TYR326 ASN322	PHE281 LEU117 ILE114 VAL277 LEU68
	Gallate epicatechin	+110.87 kcal/mol		594.1	SER319 TRP285 CYS110 SER113 TYR326	LEU68 LEU274 PHE281 VAL277 ILE114 LEU75 ILE120 LEU117
	Gallocatechin gallate	+140.55 kcal/mol		621.448	TYR326 SER113 ASN322	LEU274 ILE120 VAL277 LEU117 LEU68
	Gallocatechin	+40.63 kcal/mol		595.415	ASN322 CYS110 SER113 TYR326	VAL277 LEU75 LEU117 LEU68
	Oleic acid	+10.36 kcal/mol		604.343	-	LEU117 ALA112 TRP151 VAL277 ALA71 LEU147 ILE120

Table 3. Cont.

Ligand	Active Compound	Free Energy Binding	Inhibition constant	Surface Interaction	Molecule Interaction	
					Hydrogen Bond	Hydrophob bond
alpha adrenoceptor	Palmitic acid	+0.65 kcal/mol		537.351	CYS110	ILE200 CYS118 LEU68 LEU75 PRO196 ILE114 PHE281 LEU117
	Tamsolusin (C)	+1.74 kcal/mol		668.874	CYS280 LYS272 ILE276 SER329	ILE276 CYS280 LEU283 ILE321 ILE325 CYS328

In the adrenoceptor ligand shown that capri acid, caprylic acid, lauric acid, linoleic acid, and myristic acid has lower free binding energy than tamsulosin as a control. The five active compounds are predicted can bind spontaneously and better than finasteride as control. The active compounds that have the same hydrogen bonds as the finasteride control on the 5-alpha-reductase ligand are catechin, epigallocatechin, gallate epicatechin, and gallocatechin gallate compounds. Purinoreceptor ligands do not have the same hydrogen bound like tamsulosin and finasteride as control. Adenoreceptor do not have hydrogen bound like tamsulosin. The result of free binding energy will used to assess the spontaneity and stability of the bound.

Inhibition constant shown that only epigallocatechin gallate compound has a lower inhibition constant than finasteride at 5-alpha-reductase ligand. Epigallocatechin gallate compound predicted have a lower inhibition constant value than the control wen its binds to the ligand. The result of alpha adrenoreceptor ligand and purinoreceptor shown that all compound has high inhibition constant value compared with tamsulosin. Data of value inhibition constant will be used to assess the magnitude of the binding inhibition that affected in the protein-ligand bound shows in figure 1-3. The surface interaction of the 5 alpha reductase ligands showed that gallocatechin gallate, gallate epicatechin, and epigallocatechin gallate had higher value than the finasteride as control.

All the compound of alpha adrenoreceptor ligand has lower interaction compared with tamsulosin. The value of the surface interaction will be used to assess the probability of protein-ligand interaction as indicated by the size and molecule area.

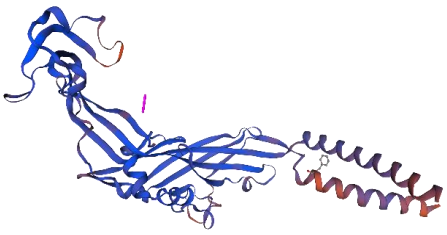

Figure 1. Crystal Structure of purinoreceptor

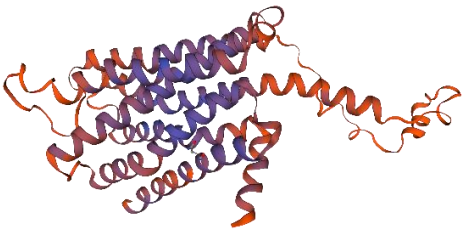

Figure 2. Crystal Structure of adrenoreceptor

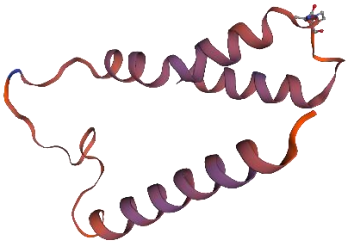

Figure 3. Crystal Structure of 5-alpha-reductase

DISCUSSION

The typical development and operation of the prostate rely on the conversion of testosterone into dihydrotestosterone (DHT) through the action of 5-alpha reductase (5-AR) enzymes, specifically types 1 and 2. There's a hypothesis suggesting that an excess of DHT could play a role in the development of both benign prostatic hyperplasia (BPH) and prostate cancer.[4]The result of docking process with 5-alpha-reductase ligand with herbs active compound showed that lowest free energy at epigallocatechin gallate. In another compound showed the value of free energy is negative but is higher than control. The amount of free energy (ΔG) are

describe the spontaneity and stability of the binding of active compound with target protein. It's suggested that epigallocatechin gallate can binding with 5-alpha-reductase ligand spontaneously and stable more than finasteride. In other compounds can also bind spontaneously, but it less reactive compared with epigallocatechin gallate compound. Herbs' active compound was predicted have ability to bind with protein target and interact spontaneously and reactively if it has a lower or equal free energy than control.[12] In every spontaneous process, increasing protein-ligand happen when there is transformation of free energy binding (ΔG) that have negative value.[13]

Inhibition constant epigallocatechin compound had lover value than control finasteride at 5-alpha-reductase ligand. Epigallocatechin gallate compound predicted has a lower inhibitory value than control when its bind to the ligand.[15] The lowest constant inhibition of free binding energy shows that ligand and target protein was bind strongly. This is due to increasing the tortional from this complex energy makes a stable complex compound and energy.[14] Decreasing value of inhibition constant indicates the smaller inhibition that occurs in increasing the ligand bound.[15]

Surface interaction value at 5-alpha-reductase ligand showed gallocatechin gallate, gallate epicatechin, and epigallocatechin gallate, oleic acid, linoleic acid, and palmitic acid has a higher value than finasteride. If the value of interaction surface higher it's shown more stable binding and give more higher biology activity.[16] Surface interaction also affected by the size of the ligand and give a higher chance for ligand and target protein to binding[16]. In this research predicted that gallocatechin gallate, gallate epicatechin, and epigallocatechin gallate compounds can bind ligand more stable and produce higher biological activity than control.

Based to the data was obtained in this research, it can conclude that the epigallocatechin gallate compound has the highest potential compared to controls and other compound to binding with 5-alpha-reductase ligands. Finasteride can inhibit 5-alpha-reductase enzyme that catalysis conversion of testosterone to the androgen dihydrotestosterone.[18] It is assume that epigallocatechin gallate has a better potential than finasteride in binding to 5-alpha-reductase ligand. The lowest free energy value, lowest inhibition constant, and high surface interaction value compared with finasteride control supported potential of epigallocatechin gallate. While other compounds have weak potential to bind with 5-alpha-reductase ligands.

Hydrogen bonds between ligand molecules and amino acids in the receptor binding pocket can significantly influence the binding energy and specificity of the interaction. For instance, studies on glycine receptor ligands have shown that hydrogen bond formation between the ligand and receptor amino acids (like lysine and aspartic acid) can estimate the binding energy, which correlates with the ligand's inhibitory activity.[17] The efficacy of ligands in inhibiting receptors can also be influenced by hydrogen bonding. Studies on the histamine H2 receptor have shown how hydrogen bond strength, affected by ligand deuteration, can alter ligand-receptor interactions, affecting agonist and antagonist binding and providing insights into receptor function and ligand efficacy.[17]

Active compound again purinoreseptor ligand

In this study used purinoreceptor ligands with tamsulosin and finasteride as control. P2X-Purinoreceptor is responsible for prostate contraction with P2X1-purinoreceptor subtype in humans[18]. Blockade of P2X1-purinoreceptors is known to inhibit electrically nerve-mediated contraction.[20] P2X1 purinoreceptor combined with α1A adrenoreceptor antagonist, may provide move effective relaxation of prostate smooth muscle.[21] Functional study in human prostate has shown that adrenoreceptor antagonists can suppress contractile response at all electric field.[22]

The result of docking with purinoreceptor ligands showed that epigallocatechin gallate compound, gallate epicatechin and gallocatechin gallate had a lower free energy value than finasteride. It is assumed that bounds formed in all compound are occur spontaneously and stable because all compounds have negative value of free energy. However, the best binding compound with the ligand is epigallocatechin gallate compound. In all compound that connected to purinoreceptor ligands, there is no compound had a lower free energy value than tamsulosin. from the data suspected that epigallocatechin gallate, gallate epicatechin and gallocatechin gallate compounds could bind strongly to purinoreceptor ligands. This is due to the low value of free binding energy is able to binding the target protein strongly and can increase potential biological activity.[23]

All inhibition constant showed that all compounds had a higher inhibitory constant value than tamsulosin. In this research predicted that the inhibition at formation protein-ligand interaction is greater than control-ligands. Because of constants inhibition show a greater barrier between ligand and protein target. The lower value inhibition constants indicate the smaller inhibition that occurs in the protein-ligand bound.[16]

The surface interaction showed that gallocatechin gallate, oleic acid and palmitic acid compounds had higher values than tamsulosin. The result indicated that gallocatechin gallate, oleic acid, and palmitic acid compound have potential to bind ligands stably. Increasing surface interaction will increase the docking stability.[24] In this research predicted that the value of surface interaction is depend on the size of molecule and the surface area of the ligand molecule, this causes a higher chance of bounding between the ligand and the compound. The binding of ligands with large hydrophobic areas to enzyme active sites often results in increased stability due to the exclusion of water molecules from the binding interface.[25]

Active compound against alpha adrenoreceptor ligands

This study uses tamsulosin as control. Tamsulosin is a selective antagonist adrenoreceptor α1 with a greater selective for prostate tissue (1A-adrenoceptor dominant) than for vascular tissue (1B dominant). Mechanism's action of tamsulosin is blocking 1A adrenoceptors in the prostate gland. Inhibit smooth muscle contraction and promotes dynamic micturition as well as increase the urinary flow rate (Qmax).[26] Blockade of adrenoceptor

α1A and α1D in the bladder result in inhibit of detrusor muscle contraction, reduced detrusor muscle instability and reduce storage symptoms.[27] Study in human prostate have shown that the contractile response to electrical field stimulation is almost completely suppressed by adrenoceptor antagonists.[19]

Data in this research shown that drug as a control had a positive free energy. Meanwhile, the ligand bounds with capric acid, caprylic acid, lauric acid, linoleic acid and myristic acid compounds have negative free energy. In every spontaneous process bounding of protein-ligand happen if there is change of free energy gibbs (ΔG) at negative system when system reach equilibrium state or constant temperature.[28] Because of the degree of protein-ligand association determined by the negative value of free energy (ΔG), determined complex stability of certain protein-ligand, or as alternative, affinity increasing ligand to certain acceptor. Therefore, the researchers suspected that the binding occur in the control and ligand was not spontaneous and less stable.

Inhibition constant showed that all compounds had a higher inhibition constant value than the tamsulosin. It is assumed that inhibition in the formation of protein-ligand interaction is greater than control-ligand. Because of the value of the inhibition constants indicate the magnitude of the barrier between the ligand and the target protein. Lower value of inhibition constant indicates the smaller inhibition that occurs in the protein-ligand bound.[15]

The value of surface interaction shown all compound had a lower value than tamsulosin. its suggested that there is potential of the compound to bound ligand less stable than control. This is due to the value of surface interaction showed that the bounding is more stable and there is a higher biology activity [16]. Surface interaction are also influenced by the size of the ligand molecule, the large of surface are, the higher chance for bounding between the ligand and the target protein.[18]

Based on all this data, we can conclude that capric acid, caprylic acid, lauric acid, linoleic acid, and myristic acid have the potential to bind to alpha adrenoreceptor ligand. All of those compounds meet the criteria of Lipinski's Rule of Five. Lipinski's Rule of Five provides valuable guidelines for assessing the oral bioavailability of compounds but does not directly address drug toxicity. However, there is a relationship between the physicochemical properties defined by these rules and potential toxicity. Several drugs that violate Lipinski's rules are still effective, particularly those designed for specific targets or used in non-oral delivery methods, which may bypass some toxicity concerns.[29]

When the compound binds to alpha adrenoreceptor ligand, it's predicted that 1A Adrenoceptor blockade prostate gland and will inhibit smooth muscle contraction. Meanwhile, blockade of 1A and 1D adrenoreceptors in the bladder will inhibit detrusor muscle contraction.[19] Lipinski's Rule of Five has significantly shaped the field of medicinal chemistry by providing a simple and effective filter for assessing drug-likeness.[30] However, its limitations necessitate the development of more comprehensive models and guidelines to enhance drug discovery and accommodate a broader range of therapeutic agents.[30]

CONCLUSION

Camellia sinensis' active compounds, such as epigallocatechin gallate, were predicted to potentially affect benign prostatic hyperplasia by targeting the protein 5-alpha-reductase. Additionally, compounds like gallocatechin gallate, oleic acid, and palmitic acid were predicted to have similar effects on the protein purinoreceptors. *Serenoa repens*' active compounds, including capri acid, caprylic acid, lauric acid, linoleic acid, and myristic acid, were also suggested to potentially impact benign prostatic hyperplasia through alpha adrenoreceptors. This study presents a potential alternative for BPH treatment using natural components, which is significant due to the demand for safer treatment options with fewer side effects compared to conventional therapies. By identifying the potential of *Camellia sinensis* and *Serenoa repens* as purinoreceptor inhibitors, the study opens avenues for new insights into the mechanisms of action in BPH treatment.

ACKNOWLEDGMENTS

The authors declare that there is no funding for this research.

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