Molecular docking studies of *Alpinia galanga* metabolites against human placental aromatase for estrogen-dependent breast cancer treatment

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ABSTRACT

Breast cancer is the leading cause of cancer-related deaths among women. With the clinical success of several synthetic aromatase inhibitors (AIs) as therapeutic agents in post-menopausal estrogen receptor-positive breast cancer, natural products have been tapped in search of chemically diverse compounds with potential better effectiveness against aromatase while conferring reduced adverse effects. *Alpinia galanga* is among the Philippine native medicinal plants with extensive studies on its phytopharmacological properties yet reports on its human placental aromatase inhibitory activity remain rudimentary. Thus, a total of 119 database-derived *A. galanga* secondary metabolites was molecularly docked onto the catalytic site of human placental aromatase using the UCSF Chimera platforms according to the AutoDock Vina Broyden-Fletcher-Goldfarb-Shanno (BFGS) algorithm. Drug-likeness was assessed *in silico* using SwissADME. Of the screened compounds, galanolactone (**1**), 4-(3,4-dimethoxy-*trans*-cinnamoyl)-*trans*-cinnamic acid (**2**), isocoronarin D (**3**), quercetin (**4**), β -sitosterol (**5**), (*E*)-8 β ,17-epoxylabd-12-ene-15,16-dial (**6**), galangin (**7**), labda-8(17),12-diene-15,16-dial (**8**), 7-(4-Hydroxy-3-methoxyphenyl)-1-phenylhept-4-en-3-one (**9**), and 3,5,7-trihydroxy-4-methoxyflavanone (**10**) conferred highest binding affinities against aromatase ranging from binding energies of -8.7 to -8.0 kcal/mol with notable formed hydrogen bonds and interactions against key amino acid residues. Top-ranked compounds exhibited druggability with at most one violation of the Lipinski Rule of Five (LRO5). Overall, the study indicates the potential of top *A. galanga* secondary metabolites as promising drug pharmacophores in developing therapeutics against breast cancer.

INTRODUCTION

Cancer remains among the deadliest maladies to mankind. In women, breast cancer ranks second as the leading cause of cancer-related deaths (American Cancer Society 2020). In the Philippines, the highest breast cancer incidence in Asia is observed with 16% of all cancer cases (Kim *et al.* 2015). With a survival rate of less than 50%, it kills 300,000 lives per year (Department of Health 2021). According to Youlden and colleagues (2014), these statistics are expected to increase every year.

Human placental aromatase, a key enzyme implicated in postmenopausal estrogen receptor-positive breast cancer, catalyzes the final step in estrogen biosynthesis from the conversion of androstenedione and testosterone. Estrogens in general are known to promote cancer cell growth, proliferation, metastasis, and recurrence in hormone-dependent breast cancers. Thus, reduction of estrogen levels *via* inhibition of the catalytic activity of aromatase is recognized as one of the effective therapeutic armamentariums in breast cancer management (Amir *et al.* 2011; Lonning *et al.* 2013). Although estrogen production in the ovaries ceases after menopause, surrounding tissues continue to produce adequate concentrations to stimulate tumor growth and eventual proliferation. Globally, 50-80% of breast cancers are estrogen-dependent where tumor cell proliferation is due to estrogen binding to its receptor. Thus, estrogen receptor-positive breast cancer therapy through use of aromatase inhibitors (AIs) is widely recognized as an emerging less invasive treatment modality (Brueggemeier *et al.* 2001; Chumsri *et al.* 2011).

Figure 1. Top ranking *A. galanga* compounds **1-10** with *in silico* inhibitory activity against aromatase.

Alpinia galanga (L.) Willd. (Zingiberaceae), commonly known as *langkawas*, is a medicinal plant found in Southern Luzon provinces in the Philippines. It is also used as an Asian spice due to its aromatic odor and spicy flavor. In Chinese traditional medicine, it is used to remedy gastrointestinal ailments such as stomachache, dyspepsia and frigid gastro-vomiting (Xiao-Lu *et al.* 2009). Natural products isolated from the genus *Alpinia* have shown broad range of biological activities such as anticancer, antioxidant, antibacterial, antiviral, and cardiovascular health-promoting properties (Zhang *et al.*, 2016). Yet studies on inhibitory activities against human placental aromatase remain

rudimentary. As part of our efforts to explore natural products with anti-cancer properties (Macabeo *et al.* 2014; Macabeo *et al.* 2017; Phukhamsakda *et al.* 2019; Quimque *et al.* 2020a; Malaluan *et al.* 2022), we report herein the anti-human placental aromatase activities of *A. galanga* constituents through molecular docking studies (Figure 1).

MATERIALS AND METHODS

Ligand selection and preparation

A library of 119 secondary metabolites previously identified from *Alpinia galanga* was screened against human placental aromatase (Appendix Figure I). The ligands in SMILES notation were converted to SYBYL mol2 file format and optimized in Avogadro (version 1.2.0). The prepared ligands were added to UCSF Chimera (version 1.14) for molecular docking (Magpantay *et al.* 2021).

Target protein preparation and minimization

The crystallized three-dimensional structure of human placental aromatase in complex with androstenedione (PDB ID: 3EQM, chain A) was fetched from the Protein Data Bank (<https://www.rcsb.org/>) using UCSF Chimera (version 1.14) (Leechaisit *et al.* 2019; de Leon *et al.* 2021). Non-standard residues, co-crystallized ligands and water molecules were removed to clear the active pocket. Protein minimization was performed using the steepest descent method in tandem with the conjugate gradient method protocol. A total of 100 steps (step size at 0.02 Angstrom) was utilized. Charges were obtained based on Amber's Antechamber module computation using the Gasteiger charge mode (Wang *et al.* 2006; Fernandez *et al.* 2021).

Molecular docking studies

Prepared ligands **1–119** in mol2 format was inputted to UCSF Chimera together with the minimized protein (Pettersen *et al.* 2004). A 3D grid box which encompasses the active site of the protein and as predicted by COACH algorithms in AutoDock Vina was generated. The actual docking was performed using Broyden-Fletcher-Goldfarb-Shanno (BFGS) algorithm. Visualization of docked complexes was carried out in BIOVIA Discovery Studio (version 4.1) (Yang *et al.* 2013).

Drug-likeness, ADME and pharmacokinetic profile

Absorption, distribution, metabolism and excretion (ADME) properties of top compounds were computationally predicted using SwissADME (<http://www.swissadme.ch/index.php>). Pharmacokinetic profiles of compounds were evaluated according to Lipinski's rule of five which determines drug-likeness based on the following criteria: molecular weight < 500, calculated lipophilicity (MLogP) < 5, number of hydrogen-bond acceptors < 10, and number of hydrogen bond acceptors < 5 (Macabeo *et al.* 2020; Quimque *et al.* 2020b).

RESULTS AND DISCUSSION

A total of 119 secondary metabolites from *Alpinia galanga* which include polyphenolics, diterpenoids, flavonoids, sterols, cinnamic acids and alkaloids were molecularly docked onto the androstenedione-binding active domain of aromatase (Appendix Table I).

Molecular docking against human placental aromatase

Molecular docking was performed to investigate binding modalities of the *Alpinia galanga* compounds and the target protein, human placental aromatase. Inhibition of aromatase is a crucial modality in the prevention of growth stimulation effect of estrogens in postmenopausal breast cancer. So, aromatase inhibitors have been investigated and developed as anti-breast cancer therapeutics. Generally, two types of AIs are known and are classified based on their mechanism of action – steroidal and nonsteroidal AIs. The latter bind reversibly to the active site *via* noncovalent bonds while the former one may interact to the active site through competitive manner *via* covalent interactions (Yadav *et al.* 2015; Adhikari *et al.* 2017).

In our study, the top ten *A. galanga* compounds exhibited binding energies ranging from -8.7 kcal/mol to -8.0 kcal/mol (Table 1). The drug control androstenedione showed -9.4 kcal/mol binding energy (Appendix Table I). Diterpenoid galanolactone (**1**) conferred the highest binding affinity. Its non-methylated cyclohexyl moiety (ring B) interacted with Val373 and Val370 *via* alkyl interactions. The fused ring A cyclohexyl group and its dimethyl group also showed alkyl interactions with Cys437. Both Ala306 and Ile133 formed alkyl bonding with the furanone moiety (Figure 2).

Table 1. Binding affinities and interacting residues of *A. galanga* compounds against aromatase.

Compound	Binding affinity (kcal/mol)	Hydrogen bond	Other Interactions
galanolactone (1)	-8.7	None	Val373, Ala306, Ile133, Val370, Cys437 (alkyl)
4-(3,4-dimethoxy- <i>trans</i> -cinnamoyl)- <i>trans</i> -cinnamic acid (2)	-8.4	Met374, Gly439	Ala306 (pi-sigma), Leu477, Val370, Cys437, Leu152, Ile132, Ile133, Phe148 (alkyl, pi-alkyl)
isocoronarin D (3)	-8.5	None	Ile132, Ala438, Phe148, Cys437, Ile133, Ala306, Trp224 (alkyl, pi-alkyl), Leu477, Leu372 (hydrophobic)
quercetin (4)	-8.3	Met374	Ile133 (pi-sigma), Ala438 (pi-alkyl)
β -sitosterol (5)	-8.3	Cys437	Ile133, Val370, Ala438, Ile132, Met303, Ala307, Phe203, Leu152, Phe148, Ala306 (alkyl, pi-alkyl)
(<i>E</i>)-8 β ,17-epoxylabd-12-ene-15,16-dial (6)	-8.3	Arg115, Met374	Ala306, Ile133, Cys437, Phe148, Ala438, Ile132 (alkyl, pi-alkyl)
galangin (7)	-8.2	Arg115, Leu372	Phe134, Trp224 (pi-pi), Ile133 (pi-sigma), Ala306 (pi-alkyl)
labda-8(17),12-diene-15,16-dial (8)	-8.1	Met374, Arg115	Cys437, Ala306, Ile133, Trp224, Phe221 (alkyl, pi-alkyl)
7-(4-hydroxy-3-methoxyphenyl)-1-phenylhept-4-en-3-one (9)	-8.1	Ala438	Ala306 (pi-sigma), Ala307, Phe148, Cys437, Ile113, Leu152 (alkyl, pi-alkyl)
3,5,7-trihydroxy-4-methoxyflavanone (10)	-8.0	Asp309, Arg115, Met374, Leu477	Ile133 (pi-sigma), Phe134 (pi-pi stacked), Ala306 (pi-alkyl)

Figure 2. Docked poses of (a) galanolactone (**1**), (b) 4-(3,4-dimethoxy-*trans*-cinnamoyl)-*trans*-cinnamic acid (**2**), (c) isocoronarin D (**3**), (d) quercetin (**4**), (e) β -sitosterol (**5**), (f) (*E*)-8 β ,17-epoxylabd-12-ene-15,16-dial (**6**), (g) galangin (**7**), (h) labda-8(17),12-diene-15,16-dial (**8**), (i) 7-(4-Hydroxy-3-methoxyphenyl)-1-phenylhept-4-en-3-one (**9**), and (j) 3,5,7-trihydroxy-4-methoxyflavanone (**10**) against aromatase (PDB ID: 3EQM).

Table 2. Summary of key amino acid domains in the active site and side residues of aromatase (Park *et al.* 2013).

Location	Type of Interaction	Key Amino Acids
Active Site	-	Met107, Arg115, Ile132, Ile133, Phe134, Trp141, Arg145, Phe148, Leu152, Leu188, Arg192, Val214, Ile217, Gln218, Tyr220, Phe221, Asp222, Trp224, Gln225, Leu228, Glu302, Met303, Ile305, Ala306, Ala307, Pro308, Asp309, Thr310, Met311, Ser312, Val313, Ser314, Val369, Val370, Asp371, Leu372, Val373, Met374, Arg375, Ile398, Pro429, Phe430, Phe432, Arg435, Glu436, Phe437, Ala438, Ala443, Leu477, Ser478, Leu479, and His480
	Hydrogen Bond	Met374, Leu372, Arg115, Thr310, Ala306, Leu377, Asp309, Leu479, and Ser478
Side Residues	Van der Waals	Phe134, Phe221, Trp224, Ile305, Ala306, Val370, Val373, Met374, Leu477

(-) = not specified

Previous studies have identified key interacting amino acids for ligands in the aromatase active site such as Met374, Arg115, Ile133, Phe134, Phe221, Trp224, Ala306, Thr310, Asp309, Val370, Val373, Leu477, and Ser478 (Ghosh 2009; Roy & Roy 2010). A more recent study added more key residues in both the active site and its periphery with

specified side residues that need to be involved in hydrogen bonding to confer inhibitory activity (Park *et al.* 2013) (Table 2).

Comparing the data on key amino acid residues by Park and colleagues (2013) and the results of our interaction analysis, 3,5,7-trihydroxy-4-methoxyflavanone (**10**) displayed the most hydrogen bonding to the key domains with four hydrogen bonds, followed by (*E*)-8 β , 17-epoxylabd-12-ene-15, 16-dial (**5**) and labda-8(17),12-diene-15,16-dial (**8**) with two hydrogen bonds. 4-(3,4-dimethoxy-*trans*-cinnamoyl)-*trans*-cinnamic acid (**2**), isocoronarin D (**3**), quercetin (**4**), and galangin (**7**) formed only one hydrogen bond whereas no hydrogen bonding was noted for galanolactone (**1**), β -sitosterol (**12**), and 7-(4-Hydroxy-3-methoxyphenyl)-1-phenylhept-4-en-3-one (**9**). In addition, compounds **1**, **2**, **7**, and **8** yielded four interactions with the side chain residues, followed by compounds **3** and **5** with three interactions, **6**, **9**, and **10** with two interactions, and lastly compound **4** with only one interaction.

Overall, seven of the ten top-ranking compounds displayed at least one hydrogen bond to the key amino acid residues on the active site of aromatase while all ten compounds showed at least one interaction with the side residues. Several residues in the active pocket also bound to the top ligands either *via* alkyl, *pi*-alkyl, or hydrophobic interactions. These interactions are prerequisites for the specific binding of a ligand to aromatase which may elicit a biological activity. It can be suggested that these compounds may bind to the active site and nearby pockets and possibly induce changes in the sensitive molecular structures which may interfere with the intricate process of aromatization, thereby inhibiting production of estrogens and consequently lowering the risk of

developing hormone-sensitive breast cancer in postmenopausal women (Park *et al.* 2013; de Leon *et al.* 2021; Giampetro *et al.* 2021).

***In silico* ADME, pharmacokinetic profiling, and drug-likeness analysis**

To assess druggability of top compounds, their ADME and pharmacokinetic profiles were predicted *in silico*. All top-binding compounds were highly druggable as correlated with their favorable ADME (absorption, distribution, metabolism, excretion) results with at most one violation to Lipinski's rule of five. Meanwhile, four compounds (**2**, **4**, **7**, and **10**) showed non-permeability to the blood-brain barrier. All ten compounds except β -sitosterol (**5**) exhibited high gastrointestinal absorption, and good fat solubility properties (Figure 3, Table 3).

Figure 3. BOILED-Egg of top-ranking compounds showing blood-brain barrier permeability and predicted human intestinal absorption of top-ranking compounds.

Table 3. Drug-likeness and pharmacokinetic profile of top compounds according to Lipinski's rule of five.

Cpd #	Molecular Weight (<500 g/mol)	H-bond donors (<5)	H-bond acceptors (<10)	Lipophilicity (MLogP<5)	Lipinski violations	Drug-likeness	Pharmacokinetic absorption/permeability	
							GI	Blood Brain Barrier
1	318.45	0	3	3.75	None	Yes	High	Yes
2	338.35	1	5	2.34	None	Yes	High	Yes
3	318.45	1	3	3.66	None	Yes	High	Yes
4	302.24	5	7	-0.56	None	Yes	High	No
5	414.71	1	1	6.73	1 (MLogP)	Yes	Low	No
6	318.45	0	3	2.85	None	Yes	High	Yes
7	270.24	3	5	0.52	None	Yes	High	No
8	302.45	0	2	3.64	None	Yes	High	Yes
9	310.39	1	3	3.36	None	Yes	High	Yes
10	302.28	3	6	0.15	None	Yes	High	No

CONCLUSION

This study reported the *in silico* inhibitory activity of the constituents of the Philippine medicinal plant *Alpinia galanga* against human placental aromatase, a pharmaceutical target in estrogen-dependent breast cancer. Results of molecular docking studies indicate the potential of *A. galanga* phytoconstituents namely galanolactone (**1**), 4-(3,4-dimethoxy-*trans*-cinnamoyl)-*trans*-cinnamic acid (**2**), isocoronarin D (**3**), quercetin (**4**), β -sitosterol (**5**), (*E*)-8 β ,17-epoxylabd-12-ene-15,16-dial (**6**), galangin (**7**), labda-8(17),12-diene-15,16-dial (**8**), 7-(4-Hydroxy-3-methoxyphenyl)-1-phenylhept-4-en-3-one (**9**), and 3,5,7-trihydroxy-4-methoxyflavanone (**10**) for discovering new anti-breast cancer agents and their proposed binding mechanisms in the target protein active site and its side residues. All compounds were also predicted *in silico* to be highly druggable. The present study also corroborates with previously reported *in vitro* pro-apoptotic effects of *A. galanga* ethanolic extracts against a breast cancer-derived cell line in a concentration- and time-dependent manner (Samarghandian *et al.* 2014). Considering the overall results, *A. galanga* compounds may serve as natural product-based templates for new generation aromatase inhibitors.

STATEMENT ON CONFLICT OF INTEREST

None

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