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Evaluation of *in silico* anticancer activity of bioactive compounds of black ginger as VEGFR2 inhibitors

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ABSTRACT

The main components of black ginger (Kaempferia parviflora Wall ex Baker.) show diverse biological effects, especially potential anticancer activity. Thirty-five bioactive compounds were screened for anticancer activity by molecular docking with AutoDock Vina software on VEGFR2 kinase. Five bioactive compounds of black ginger showed the strongest interaction with VEGFR2 target, especially stronger than the reference drug Axitinib (-9.2 Kcal/mol) including 5-Hydroxy-7,4'-dimethoxyflavanone (-9.9 Kcal/mol), Kaempferide (-9.7 Kcal/mol), 5-Hydroxy-7-methoxyflavone (-9.6 Kcal/mol), Genkwanin (-9.6 Kcal/mol), and Sakuranetin (-9.5 Kcal/mol). Kaempferide formed the most hydrogen bonds on VEGFR2 kinase with four strong hydrogen bonds (1.76-2.86 Å) and one carbon-hydrogen bond (3.78 Å). The hydrogen bonds are formed at the hydroxy (-OH) and methoxy (-OCH_3) groups of these phytocompounds. In particular, these bioactive compounds all demonstrated hydrogen bond formation, hydrogen bond length, and hydrophobic interactions at levels equal to or better than the reference drug Axitinib. Therefore, these compounds could be potential molecules to develop new anticancer drugs on the VEGFR2 target.

Keywords: *black ginger, anticancer, in silico, molecular docking, VEGFR2*

1. INTRODUCTION

Cancer incidence and mortality are increasing worldwide. Therefore, active ingredients for cancer treatment derived from natural ingredients are being explored to develop new cancer drugs. *Kaempferia parviflora* Wall ex Baker, also known as black ginger (BG), is a plant in the Zingiberaceae family that has many pharmacological effects such as neuroprotection, antibiotic, anti-allergy, anti-obesity, anti-stress, antibacterial, antifungal, antidiabetic, anti-inflammatory, and anti-cancer [1, 2]. The main components of the genus *Kaempferia* were essential oils, diterpenes, phenolic compounds, sterols, and flavonoids [3]. BG is commonly used in traditional drinks and as the primary raw material for traditional medicinal preparations. In particular, BG contains many potential bioactive compounds that can be developed into anticancer and anti-metastatic drugs.

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Vascular endothelial growth factor receptor 2 (VEGFR2) is a major responder to vascular endothelial growth factor signaling and is overexpressed in neovascular tumor endothelial cells in comparison to normal endothelial cells. VEGFR2 is activated after the binding of VEGF, which initiates a phosphorylation process that results in an enhancement of endothelial cell proliferation and migration [4]. Therefore, VEGFR2 inhibitors are tyrosine kinase receptor inhibitors that reduce angiogenesis or lymphangiogenesis, leading to anticancer activity. VEGF inhibitors utilized in oncologic care include bevacizumab, sorafenib, sunitinib, nilotinib, pazopanib, and dasatinib.

Many studies have documented the anticancer activity of BG extracts and active ingredients using *in vitro* and *in vivo* tests [2, 3, 5, 6]. Moreover, study data on the mechanism of action of bioactive compounds of BG on VEGFR2 are also limited.

Therefore, this *in silico* study aimed to identify active ingredients with strong or potential effects on the VEGFR2 target for anticancer activity.

2. METHOD

2.1. Ligand preparation

The structures of the active ingredients of BG were downloaded from the PubChem database of NLM (National Library of Medicine). The structure of new ligands was drawn in ChemBioDraw Ultra 19. The energy of these ligands was minimized using ChemBio3D Ultra 19 software [7, 8].

2.2. Protein preparation

The crystal structure of the VEGFR2 kinase domain in complex with Axitinib (PDB ID: 4AG8) was retrieved from the protein data bank (rcsb.org) (Figure 1). All the water molecules were removed from VEGFR2 kinase. Then, VEGFR2 kinase was added to only polar hydrogen and Kollman charges. The grid box for docking simulations was set by AutoDock tools (Table 1).

Table 1. Grid box parameters for VEGFR2 kinase

Target	Size			Center		
	x	y	z	x	y	z
VEGFR2	40	40	40	20.8237	25.5351	39.4596

VEGFR2 - Vascular endothelial growth factor receptor 2, exhaustiveness = 8, num modes = 10, energy range = 4

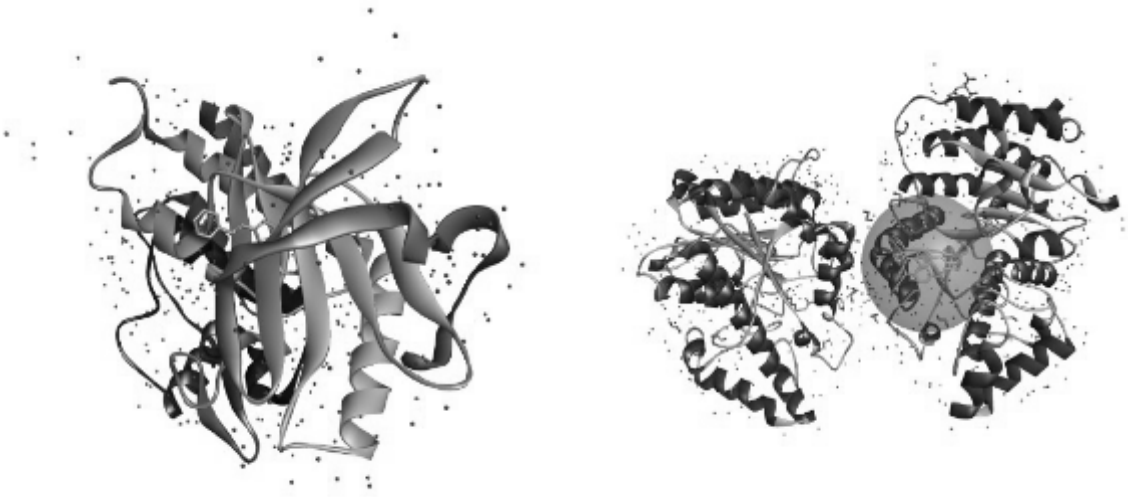


Figure 1. Structure and active site of VEGFR2 kinase

2.3. Molecular docking

The ligands were docked with the target to determine the docking parameters using AutoDock Vina docking simulation protocol (AMBER force field) with the help of Grid-based ligand docking and partial charges were automatically calculated. The search algorithm of AutoDock Vina is a Monte-Carlo iterated search combined with the BFGS17 gradient-based optimizer with a united-atom scoring function that combines knowledge-based and empiric scoring function features as well as supports the AutoDock4.2 scoring function. AutoDock Vina was compiled and run under Windows 10.0 Professional operating system. Discovery Studio 2021 was used to deduce the pictorial representation of the interaction between the ligands and the target protein [9, 10].

3. RESULTS AND DISCUSSION

Thirty-five bioactive compounds of BG were screened from published studies on active ingredient isolation [1-3, 5, 6], and *in vitro* anticancer evaluation (Table 2 and Figure 2). The interaction study of these phytocompounds with VEGFR2 kinase was carried out to determine the optimal structure compared to the anticancer drug Axitinib and co-crystallized ligand of the target (Table 2). The docking results of the receptor-ligand interaction are shown in Tables 2 and 3 and Figure 3 and 5. Structure of phytocompounds with potential *in silico* VEGFR2 kinase inhibitory activity is shown in Figure 4.

Table 2. The *in silico* binding affinity of ligands with VEGFR2 kinase

Entry	Compound	Binding Affinity (Kcal/mol)
1	5-Hydroxy-7,4'-dimethoxyflavanone	**-9.9**
2	Kaempferide	**-9.7**
3	5-Hydroxy-7-methoxyflavone	**-9.6**
4	Genkwanin	**-9.6**
5	Sakuranetin	**-9.5**
6	Viscumneoside VI	-9.4
7	Tectochrysin	-9.3
8	KP1	-9.2
9	Acacetin 7-galactoside	-9.0
10	4',5,7-Trimethoxyflavone	-8.9
11	Demethoxyyangonin	-8.8
12	5,7-Dimethoxyflavone	-8.7
13	3',4',5,7-Tetramethoxyflavone	-8.6
14	KP5	-8.6
15	KP2	-8.4
16	1,3-Dihydroxy-2-ethoxymethyl-anthraquinone	-8.3
17	5,3‘-Dihydroxy-3,7,4‘-trimethoxyflavone	-8.2
18	1,4-Dihydroxy-2-ethoxymethylanthraquinone	-8.0
19	2‘-Hydroxy-4‘,6‘-dimethoxychalcone	-7.9
20	Panduratin A	-7.9
21	3,5,7,3',4'-Pentamethoxyflavone	-7.8
22	5-Hydroxy-3,7,3‘,4‘-tetramethoxyflavone	-7.8
23	5-Hydroxy-3,7,4‘-trimethoxyflavone	-7.8
24	5-Hydroxy-3,7-dimethoxyflavone	-7.8
25	Kaempferide 3-O-glucoside	-7.7
26	Retusine	-7.6
27	Denbinobin	-7.6
28	3,5,7-Trimethoxyflavone	-7.6
29	Tangeretin	-7.6
30	KP3	-7.6
31	5-Hydroxy-4,7-dimethoxyflavanone	-7.5
32	Nobiletin	-7.4
33	4-Hydroxypanduratin A	-7.4
34	3,5,7,4'-Tetramethoxyflavone	-7.3
35	KP4	-7.3
36	**Axitinib**	**-9.2**
37	**Co-crystallized ligand**	**-11.0**

Bioactive compounds of BG showed good interactions with VEGFR2 kinase with an affinity between -7.3 and -9.9 Kcal/mol. Co-crystallized ligand of VEGFR2 showed the highest affinity (-11.0 Kcal/mol). Meanwhile, compounds including 5-Hydroxy-4',7-dimethoxyflavanone, Kaempferide, 5-Hydroxy-7-methoxyflavone, Genkwanin, Sakuranetin, Viscumneoside VI, Tectochrysin, and KP1 (-9.2 to -9.9 Kcal/mol) exhibited good binding affinity with VEGFR2 compared to the reference drug Axitinib (-9.2 Kcal/mol). Five phytocompounds of BG showed the strongest interaction with VEGFR2 kinase, especially stronger than the reference drug Axitinib including 5-Hydroxy-7,4'-dimethoxyflavanone (-9.9 Kcal/mol), Kaempferide (-9.7 Kcal/mol), 5-

Hydroxy-7-methoxyflavone (-9.6 Kcal/mol), Genkwanin (-9.6 Kcal/mol), and Sakuranetin (-9.5 Kcal/mol). The structures of these bioactive compounds are shown in Figure 3.

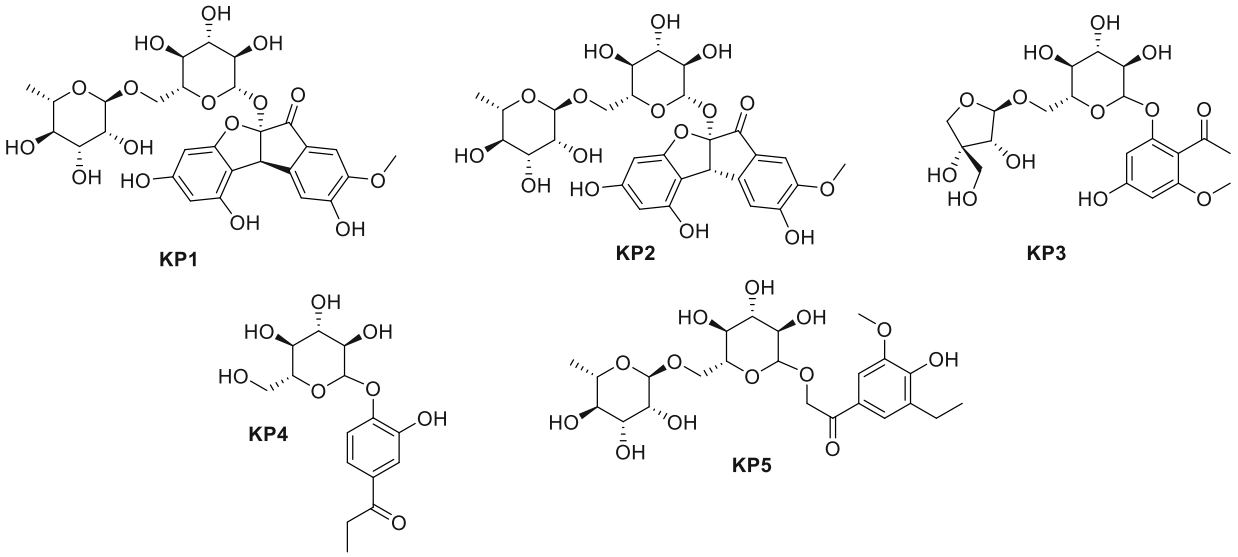


Figure 2. Structure o phytocompounds KP1-KP5

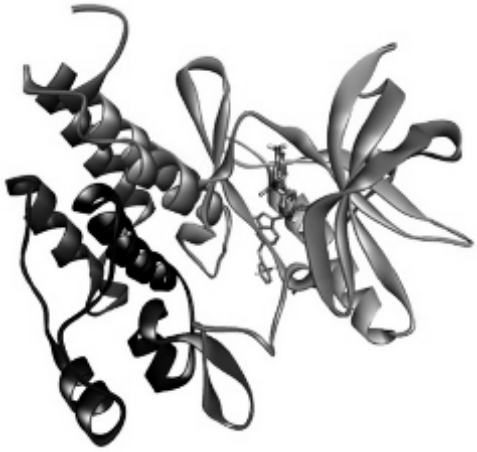


Figure 3. Interaction sites of potential ligands on VEGFR2 kinase

Table 3. Molecular docking results of potential phytocompounds and reference drug

Ligand	Affinity (Kcal/mol)	Distance (Å)	Bond category	Bond types	Amino acid
5-Hydroxy-4',7-dimethoxy flavanone	-9.9	3.00	HB	Conventional HB	LYS868
		1.87	HB	Conventional HB	CYS919
		3.97	Hydrophobic	π-σ	LEU840
		3.97	Hydrophobic	π-σ	LEU840
		4.00	Hydrophobic	π-σ	LEU1035
		4.41	Other	π-Sulfur	CYS1045
		4.76	Hydrophobic	π-π T-shaped	PHE1047
		5.10	Hydrophobic	Alkyl	VAL899
		4.12	Hydrophobic	Alkyl	VAL916
		4.61	Hydrophobic	Alkyl	LEU840
		5.36	Hydrophobic	π-Alkyl	VAL848

Ligand	Affinity (Kcal/mol)	Distance (Å)	Bond category	Bond types	Amino acid
		4.80	Hydrophobic	π-Alkyl	ALA866
		4.15	Hydrophobic	π-Alkyl	VAL848
		4.95	Hydrophobic	π-Alkyl	ALA866
		5.49	Hydrophobic	π-Alkyl	LEU1035
Kaempferide	-9.7	2.66	HB	Conventional HB	LYS868
		1.76	HB	Conventional HB	CYS919
		2.86	HB	Conventional HB	GLU917
		2.09	HB	Conventional HB	LEU840
		3.78	HB	Carbon HB	GLU885
		3.65	Hydrophobic	π-σ	LEU840
		3.95	Hydrophobic	π-σ	LEU840
		3.98	Hydrophobic	π-σ	LEU840
		3.96	Hydrophobic	π-σ	VAL848
		4.86	Hydrophobic	π-π T-shaped	PHE1047
		5.13	Hydrophobic	Alkyl	VAL899
		4.59	Hydrophobic	Alkyl	VAL916
		5.34	Hydrophobic	π-Alkyl	VAL848
		4.68	Hydrophobic	π-Alkyl	ALA866
		4.57	Hydrophobic	π-Alkyl	LEU1035
		4.93	Hydrophobic	π-Alkyl	ALA866
		4.45	Hydrophobic	π-Alkyl	CYS1045
5-Hydroxy-7-methoxy flavone	-9.6	1.88	HB	Conventional HB	CYS919
		1.95	HB	Conventional HB	CYS919
		3.94	Hydrophobic	π-σ	LEU840
		3.90	Hydrophobic	π-σ	VAL848
		4.74	Hydrophobic	π-π T-shaped	PHE1047
		5.27	Hydrophobic	π-Alkyl	VAL848
		4.71	Hydrophobic	π-Alkyl	ALA866
		4.60	Hydrophobic	π-Alkyl	LEU1035
		3.79	Hydrophobic	π-Alkyl	LEU840
		4.96	Hydrophobic	π-Alkyl	ALA866
		4.46	Hydrophobic	π-Alkyl	CYS1045
Genkwanin	-9.6	1.74	HB	Conventional HB	CYS919
		1.86	HB	Conventional HB	CYS919
		3.73	Hydrophobic	π-σ	LEU840
		3.95	Hydrophobic	π-σ	LEU1035
		4.25	Other	π-Sulfur	CYS1045
		4.75	Hydrophobic	π-π T-shaped	PHE1047
		4.79	Hydrophobic	Alkyl	LEU840
		4.47	Hydrophobic	π-Alkyl	LEU840
		5.39	Hydrophobic	π-Alkyl	VAL848

Ligand	Affinity (Kcal/mol)	Distance (Å)	Bond category	Bond types	Amino acid
		4.73	Hydrophobic	π-Alkyl	ALA866
		4.30	Hydrophobic	π-Alkyl	VAL848
		5.14	Hydrophobic	π-Alkyl	ALA866
		5.44	Hydrophobic	π-Alkyl	VAL899
		5.48	Hydrophobic	π-Alkyl	LEU1035
Sakuranetin	-9.5	1.78	HB	Conventional HB	CYS919
		4.13	HB;Other	π-Donor HB; π-Sulfur	CYS1045
		4.72	Hydrophobic	π-π T-shaped	PHE1047
		4.76	Hydrophobic	Alkyl	LEU840
		3.76	Hydrophobic	π-Alkyl	LEU840
		4.41	Hydrophobic	π-Alkyl	VAL848
		5.25	Hydrophobic	π-Alkyl	ALA866
		5.39	Hydrophobic	π-Alkyl	VAL899
		5.42	Hydrophobic	π-Alkyl	LEU1035
Axitinib	-9.2	3.75	HB	Conventional HB	CYS817
		4.22	Electrostatic	π-Cation	LYS868
		4.81	Electrostatic	π-Cation	ARG1027
		3.74	Hydrophobic	π-σ	LYS868
		3.76	Hydrophobic	π-σ	LEU889
		3.69	Hydrophobic	π-σ	VAL916
		5.00	Hydrophobic	π-Alkyl	LEU889
		5.27	Hydrophobic	π-Alkyl	VAL848
		4.44	Hydrophobic	π-Alkyl	LYS868

HB - Hydrogen Bond, Hydrophobic interaction (π-σ, π-π stacked, amide-π stacked, alkyl, π-alkyl)

All potential phytocompounds formed strong hydrogen bonds similar to the reference drug Axitinib (Figure 4 and 5). Kaempferide formed the most hydrogen bonds on VEGFR2 kinase with four strong hydrogen bonds and one carbon-hydrogen bond. In addition, compounds 5-Hydroxy-4',7-dimethoxyflavanone, 5-Hydroxy-7-methoxyflavone, and Genkwanin exhibited tưo strong hydrogen bonds while the reference drug Axitinib and Sakuranetin only formed one strong hydrogen bond. In particular, hydrogen bonds are formed at the hydroxy (-OH) and methoxy (-OCH_3) groups of these phytocompounds. These are also these groups that increase the binding affinity of the potential phytocompounds with the VEGFR2 target.

Compound 5-Hydroxy-4',7-dimethoxyflavanone exhibited two conventional/ strong hydrogen bonds at LYS868 and CYS919 amino acids with bond lengths of 3.00 and 1.87 Å, respectively. Kaempferide showed four conventional hydrogen bonds at LYS868, CYS919, GLU917, and LEU840 amino acids with bond lengths between 1.76 and 2.86 Å. In addition, compound 5-Hydroxy-7-methoxyflavone and Genkwanin exhibited two conventional hydrogen bonds at CYS919 amino acid with bond lengths in the range of 17.4-1.95 Å. However, Sakuranetin only showed one conventional hydrogen bond with a bond length of 1.78 Å at CYS919 amino acid. Meanwhile, the reference drug Axitinib also showed only one conventional hydrogen bond with a large bond length of 3.75 Å at amino acid CYS817. Therefore, the hydrogen bond of Axitinib with VEGFR2 is weaker than the hydrogen bonds of bioactive compounds of BG. On the other hand, five phytocompounds and the reference drug all exhibited hydrophobic interactions (π-σ, π-π, alkyl, and π-alkyl) with the amino acids of VEGFR2 at benzene rings. The π-Sulfur interaction with

CYS1045 was found in the compounds 5-Hydroxy-4',7-dimethoxyflavanone, Genkwanin, and Sakuranetin. In summary, these five phyto-compounds need to continue studying *in vitro* biological activity on VEGFR2 to confirm the *in silico* research results.

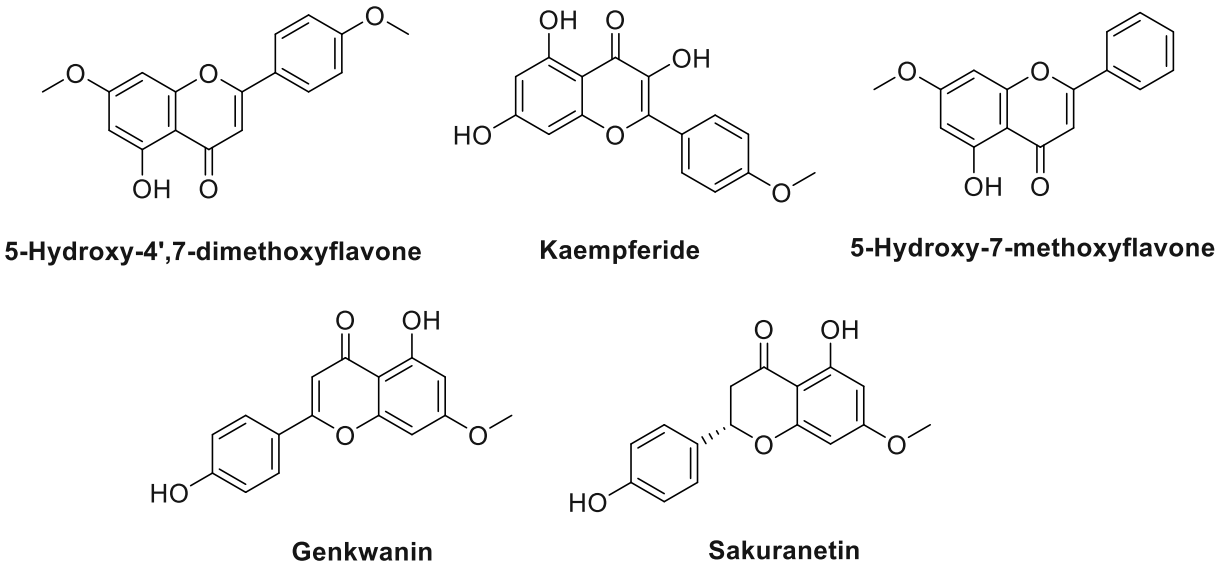
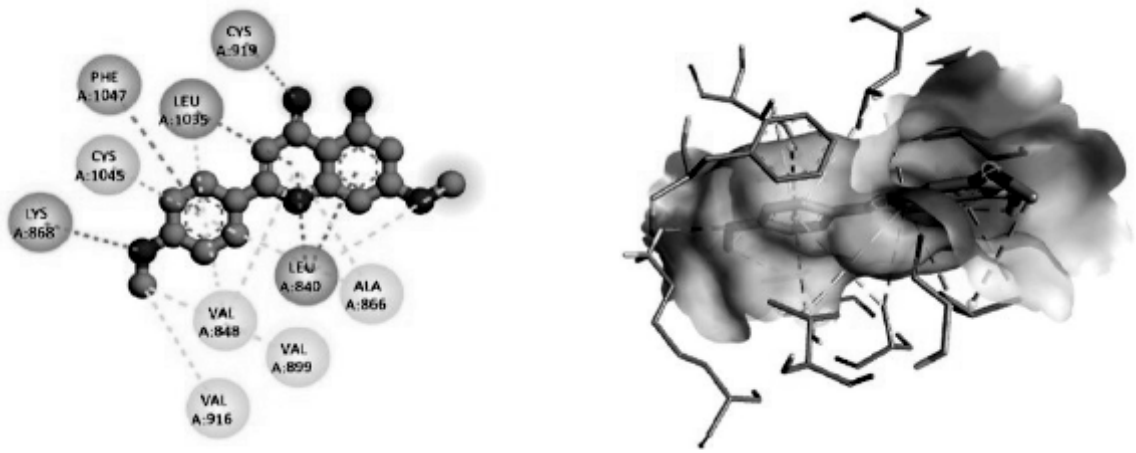
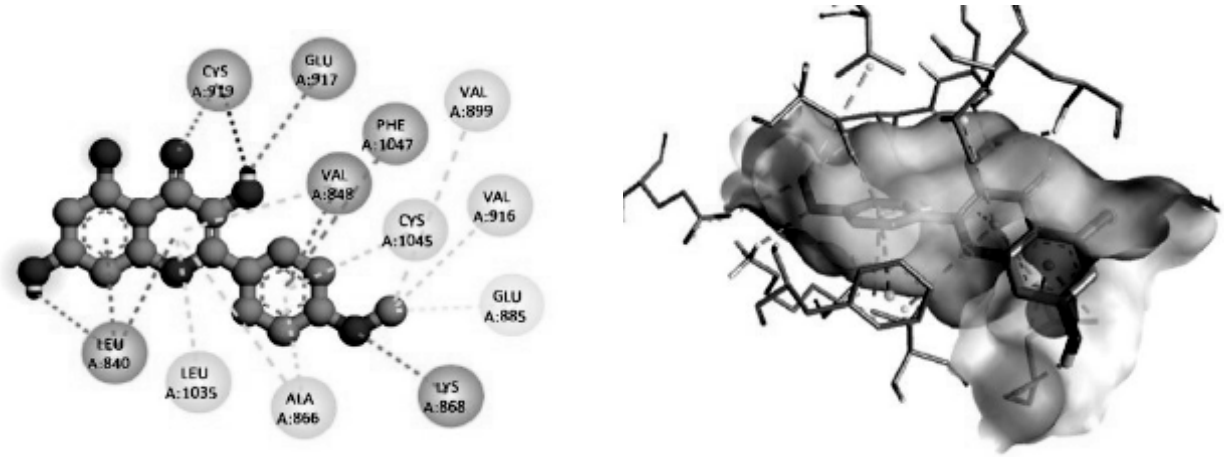


Figure 4. Phytocompounds with potential *in silico* VEGFR2 kinase inhibitory activity



5-Hydroxy-4',7-dimethoxyflavanone



Kaempferide

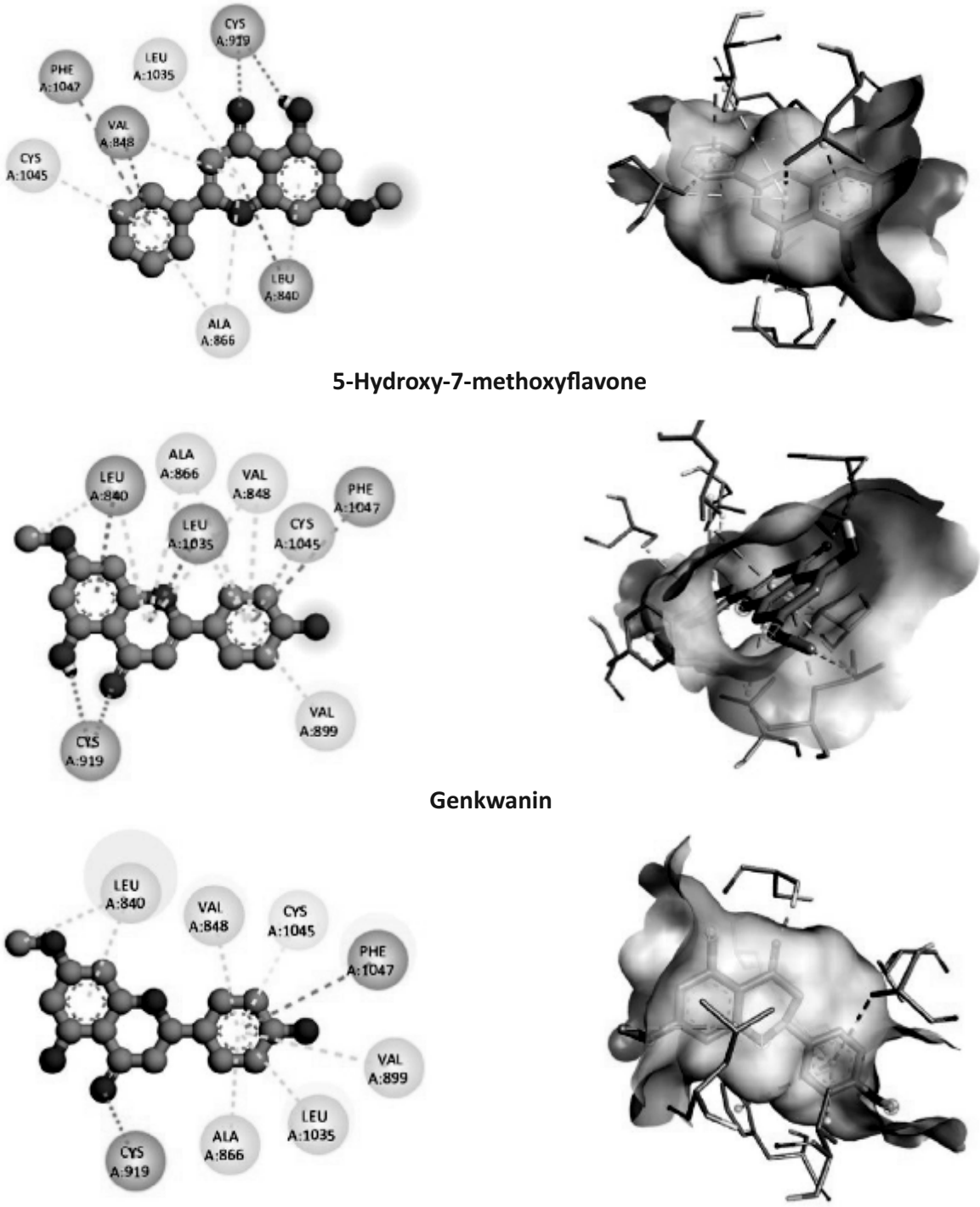


Figure 5. 2D and 3D representation of the interaction of potential phytocompounds with VEGFR2 kinase

Two compounds 5-Hydroxy-4',7-dimethoxy-flavanone and Kaempferide showed the highest number of interactions at the VEGFR2 active site with 10-12 amino acids, while three compounds 5-Hydroxy-7-methoxyflavone, Genkwanin, and Sakuranetin only exhibited 7-8 interactions with amino acids of VEGFR2 target (Figure 5). However, the type of amino acid interacting on VEGFR2 was found to be similar between these compounds at the active site (Table 4). In addition, five compounds 5-Hydroxy-4',7-dimethoxyflavanone (M.Wt = 298.2940), Kaempferide (M.Wt = 300.2660), 5-Hydroxy-7-methoxyflavone (M.Wt = 268.2680), Genkwanin (M.Wt = 284.2670) and Sakuranetin (M.Wt = 286.2830) have molecular weights and contain many elements (oxygen and

nitrogen)/functional groups (hydroxy, amide, amine, and ketone) with the ability to form hydrogen bonds with VEGFR2 similar to reference drug Axitinib (M.Wt = 386.4730). This may be the reason why phytocompound aglycones or low molecular weight molecules without sugar groups showed better interactions than other bioactive compounds of BG.

On the other hands, the most commonly used anti-angiogenesis agents target vascular endothelial cell growth factor (VEGF). Some VEGF/VEGFR inhibitors include 3-substituted indolinone compound (SU5416), sorafenib, sunitinib, pazopanib, tivozanib, axitinib, and cediranib, which have been used to treat lung, breast, gastric, liver, and renal cancers. Besides, the *in silico* docking of phytocompounds of BG was also investigated for receptors Bcl-2, Bcl-XL, ERK2, and FAK for anticancer activity. *In silico* results indicated that 5-Hydro-7,8,2'-trimethoxy-flavanone and Denbinobin are bioactive compounds responsible for the cytotoxic and anti-migration activity of BG extract. These two compounds can be potential breast cancer treatment candidates [11]. Therefore, phytocompounds of BG with potential *in silico* VEGFR2 inhibitor activity in the present study are also potential candidates that can be further studied for the treatment of various types of cancer.

4. CONCLUSION

Phytocompounds of BG showed good interactions compared to Axitinib on VEGFR2 kinase. In particular, five phytocompounds (5-Hydroxy-4',7-dimethoxyflavanone, Kaempferide, 5-Hydroxy-7-methoxyflavone, Genkwanin, and Sakuranetin) showed potential *in silico* anticancer activity with a strong binding affinity. These compounds all demonstrated hydrogen bond formation, hydrogen bond length, and hydrophobic interactions at levels equal to or better than the reference drug.

ACKNOWLEDGMENTS

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Đánh giá hoạt tính kháng ung thư *in silico* của các hoạt chất trong gừng đen như chất ức chế VEGFR2

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TÓM TẮT

Các thành phần chính của Gừng đen (Kaempferia parviflora Wall ex Baker.) cho thấy tác dụng sinh học đa dạng, đặc biệt là hoạt tính kháng ung thư tiềm năng. Ba mươi lăm hợp chất hoạt tính được sàng lọc hoạt tính kháng ung thư bằng docking phân tử với phần mềm AutoDock Vina trên VEGFR2 kinase. Năm hợp chất hoạt tính của Gừng đen cho thấy tương tác mạnh nhất với đích tác dụng VEGFR2, đặc biệt mạnh hơn thuốc đối chứng Axitinib (-9.2 Kcal/mol) gồm 5-Hydroxy-7,4'-dimethoxyflavanon (-9.9 Kcal/mol), Kaempferid (-9.7 Kcal/mol), 5-Hydroxy-7-methoxyflavon (-9.6 Kcal/mol), Genkwanin (-9.6 Kcal/mol) và Sakuranetin (-9.5 Kcal/mol). Kaempferid hình thành nhiều liên kết hydrogen nhất trên VEGFR2 kinase với bốn liên kết hydrogen mạnh (1.76-2.86 Å) và một liên kết carbon-hydrogen (3.78 Å). Liên kết hydrogen được hình thành ở nhóm hydroxy (-OH) và methoxy (-OCH_3) của các phytocompound này. Đặc biệt, các hoạt chất này đều thể hiện sự hình thành liên kết hydrogen, độ dài liên kết hydrogen và các tương tác kỵ nước ở mức bằng hoặc tốt hơn thuốc đối chiếu Axitinib. Do đó, các hợp chất này có thể là phân tử tiềm năng để phát triển các loại thuốc kháng ung thư mới trên đích tác dụng VEGFR2.

Từ khóa: *gừng đen, kháng ung thư, in silico, docking phân tử, VEGFR2*

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