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Artikel

Cinnamomum burmannii Bioactives as VEGFR–2 Inhibitors in Colon Cancer: A Chemoinformatics Approach

Senyawa Bioaktif *Cinnamomum burmannii* sebagai Inhibitor VEGFR–2 pada Kanker Kolon: Pendekatan Kemoinformatika

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Abstract

Colon cancer is among the most prevalent cancers globally, with its progression closely associated with angiogenesis, primarily mediated by the activation of vascular endothelial growth factor receptor 2 (VEGFR-2). Although VEGFR-2 inhibitors such as apatinib have demonstrated efficacy in colon cancer therapy, their clinical use is limited due to potential side effects and high treatment costs. Natural compounds from *Cinnamomum burmannii*, a species known to contain secondary metabolites including flavonoids, saponins, phenols, tannins, and sterols/triterpenoids, present a potential alternative. This study evaluated the inhibitory potential of *C. burmannii* bioactive compounds against VEGFR-2 using a computational approach. The methods comprised Lipinski's rule of five (RO5) analysis, ADMET (absorption, distribution, metabolism, excretion, and toxicity) prediction, pharmacophore screening, and molecular docking simulations. Among the screened compounds, methylhydroxychalcone emerged as the most promising candidate, exhibiting a favorable binding affinity with a Gibbs free energy of −8.51 kcal/mol and an inhibition constant of 579.80 nM. It also fulfilled drug-likeness criteria and displayed a favorable pharmacokinetic profile, although it was concurrently predicted to be mutagenic and to cross the blood–brain barrier, indicating that experimental safety validation is required. Notably, methylhydroxychalcone interacted with the Asp1046 residue on VEGFR-2, a key interaction site also targeted by apatinib. These findings support the potential of cinnamon bark-derived compounds, particularly methylhydroxychalcone, as prospective VEGFR-2 inhibitors for colon cancer therapy.

Keywords: *Cinnamomum burmannii*; colon cancer; computational studies; VEGFR-2

Abstrak

Kanker kolon merupakan salah satu jenis kanker yang paling banyak ditemukan di dunia, dengan perkembangannya yang erat kaitannya dengan angiogenesis, terutama melalui aktivasi *vascular endothelial growth factor receptor 2* (VEGFR-2). Meskipun inhibitor VEGFR-2 seperti apatinib telah terbukti efektif dalam terapi kanker kolon, penggunaannya secara klinis masih terbatas akibat efek samping dan biaya pengobatan yang tinggi. Senyawa alami dari *Cinnamomum burmannii* (kayu manis), yang diketahui mengandung metabolit sekunder seperti flavonoid, saponin, fenol,

tanin, dan sterol/triterpenoid, berpotensi menjadi alternatif terapi. Penelitian ini bertujuan mengevaluasi potensi senyawa bioaktif C. burmannii sebagai inhibitor VEGFR-2 melalui pendekatan komputasi. Metode yang digunakan meliputi analisis Lipinski's rule of five (RO5), prediksi ADMET (absorpsi, distribusi, metabolisme, ekskresi, dan toksisitas), penapisan farmakofor, dan simulasi penambatan molekul. Dari senyawa yang diuji, metilhidroksikalkon menunjukkan potensi tertinggi, dengan afinitas ikatan yang baik (energi bebas Gibbs −8,51 kkal/mol) dan konstanta inhibisi 579,80 nM. Senyawa ini juga memenuhi kriteria drug-likeness dan menunjukkan profil farmakokinetik yang baik, meskipun secara bersamaan diprediksi bersifat mutagenik dan mampu melewati sawar darah–otak, sehingga validasi keamanan secara eksperimental masih diperlukan. Metilhidroksikalkon berinteraksi dengan residu Asp1046 pada VEGFR-2, situs interaksi kunci yang juga menjadi target apatinib. Temuan ini mendukung potensi senyawa dari kulit batang kayu manis, khususnya metilhidroksikalkon, sebagai kandidat inhibitor VEGFR-2 untuk terapi kanker kolon.

Kata Kunci: Cinnamomum burmannii; kanker kolon; studi komputasi; VEGFR-2

1. INTRODUCTION

Colon cancer is characterized by uncontrolled cell division and differentiation due to cumulative genetic mutations in the epithelial cells of the colon, leading to proliferation, invasion, and metastasis [1]. It remains one of the most prevalent cancers worldwide, particularly among men. According to GLOBOCAN 2024 estimates, colon cancer ranks fourth in global incidence, with 1,206,011 new cases reported. In Indonesia, colorectal cancer is the third most frequent malignancy, accounting for 39,751 new cases (8.4% of all cancers); it ranks second among men (22,314 cases, 11.0%) and fourth among women (17,437 cases, 6.4%) [2]. The progression and metastasis of colon cancer are strongly influenced by angiogenesis, the formation of new blood vessels from pre-existing ones. Among the various proangiogenic factors, vascular endothelial growth factor (VEGF) and its receptor VEGFR-2 (also known as KDR) play a central role in this process. While VEGFR-2 is expressed at low levels in normal cells, its expression is markedly upregulated in tumor endothelial cells and several cancers, including colorectal cancer, where overexpression reaches 71.4%. This receptor also contributes to both physiological and pathological angiogenesis, including embryonic development, inflammation, and tumor growth [3,4].

Current treatment options for colon cancer include chemotherapeutic agents such as 5-fluorouracil (5-FU), oxaliplatin, and irinotecan, which target DNA replication and cell proliferation. Apatinib, a selective VEGFR-2 inhibitor, has shown potential in colon cancer therapy due to its antiproliferative and proapoptotic effects, including G0/G1 cell cycle arrest and inhibition of cell migration and invasion. It exerts its effect by inhibiting VEGFR-2 activity, thereby reducing downstream signaling pathways such as p-Src, p-Akt, and p-GSK3β, thereby suppressing β-catenin signaling and angiogenesis [5]. However, apatinib is associated with several adverse effects, including hypertension, proteinuria, hand-foot syndrome, gastrointestinal bleeding, and perforation [6]. In addition, the high cost of apatinib limits its accessibility in regions such as Indonesia, underscoring the need for safer, more affordable alternative therapies.

In recent years, herbal-based treatments have gained attention as promising alternatives due to their favorable safety profiles and bioactive potential for use as chemoprevention agents [7]. One such candidate is *Cinnamomum burmannii* (Indonesian cinnamon, locally known as *kayu manis*), which contains various secondary metabolites, including flavonoids, saponins, phenols, tannins, and sterols/triterpenoids [8]. Several studies have highlighted the anticancer potential of cinnamon and its major constituents [9], such as cinnamaldehyde (68.3–82% of the essential oil content), eugenol, and polyphenols, which are known to modulate signaling pathways involved in cell proliferation, apoptosis, and angiogenesis [10,11]. The ethanol extract of C. burmannii has demonstrated strong antioxidant activity (IC50 = 6.28 μg/mL), and cinnamaldehyde has shown cytotoxic effects against C-33A cervical cancer cells [12]. Additionally, cinnamon essential oil and ethanol extracts have shown moderate cytotoxic activity against T47D breast and HeLa cervical cancer cells and have been reported to induce apoptosis [13,14]. These findings suggest that compounds from C. burmannii may act as anticancer agents by inducing

apoptosis, inhibiting cancer cell proliferation, and preventing tumor angiogenesis. However, their specific interactions with VEGFR-2 have not been investigated. Therefore, this study explored the potential of bioactive compounds from C. burmannii as VEGFR-2 inhibitors through in silico analysis, including drug-likeness evaluation and molecular interaction studies. The results are expected to provide scientific evidence supporting the potential development of cinnamon bark as a natural anticancer agent targeting VEGFR-2.

2. MATERIALS AND METHODS

2.1. Materials

The materials used in this study consisted of the VEGFR-2 protein (PDB ID: 2P2I) and its native ligand obtained from the Protein Data Bank, a reference compound (apatinib), and 20 test compounds derived from the bioactive constituents of *Cinnamomum burmannii*, retrieved from PubChem in SMILES format (Figure 1).

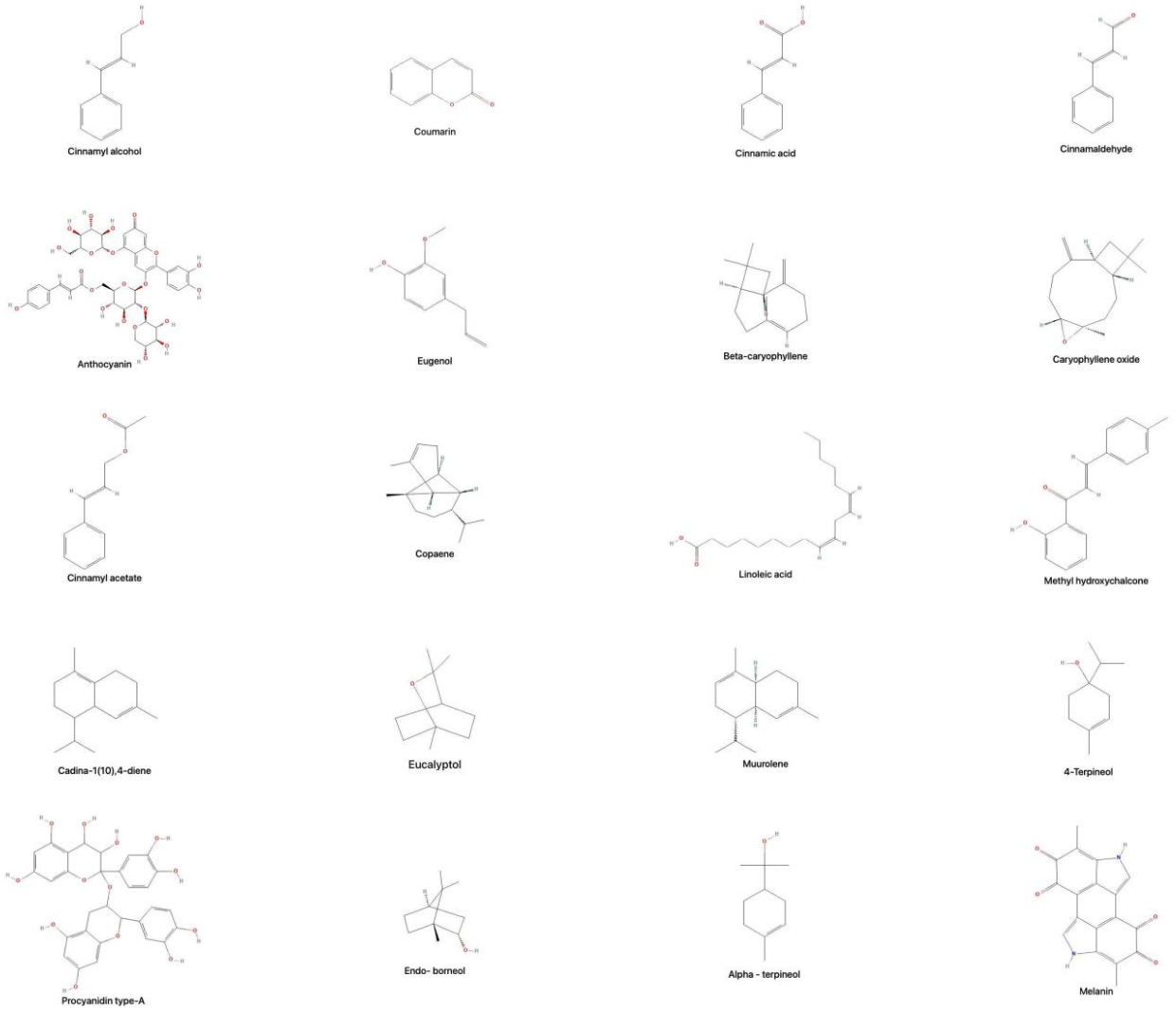


Figure 1. Chemical structures of the 20 bioactive compounds from *Cinnamomum burmannii* evaluated in this study.

2.2. Instruments

The hardware used in this study was a personal laptop equipped with an AMD A9-9425 CPU, 4 GB of DDR4 RAM, running the Windows 10 operating system. The software and web-based platforms used included PubChem, Chem3D Pro 12.0, the Protein Data Bank, MCule, PreADMET, AutoDock 4.2.6, BIOVIA Discovery Studio 2025, and LigandScout.

2.3. Procedure

The overall research procedure comprised four main stages: Lipinski's rule of five prediction, ADMET prediction, pharmacophore screening, and molecular docking simulation, as described in the following subsections.

2.3.1. Lipinski's Rule of Five Prediction

Lipinski's rule of five was used to predict the physicochemical properties of the test compounds and evaluate their potential as oral drug candidates. The two-dimensional structures of the test compounds were obtained in SMILES format from PubChem (https://pubchem.ncbi.nlm.nih.gov) and analyzed using the Mcule Property Calculator (http://mcule.com/apps/property-calculator/). Parameters assessed included molecular weight, logP, hydrogen-bond donors, and hydrogen-bond acceptors.

2.3.2. ADMET Prediction

ADMET prediction was performed to assess the pharmacokinetic properties and potential toxicity of the test compounds. The analysis was carried out using the PreADMET platform (https://preadmet.webservice.bmdrc.org/), a web-based tool for predicting absorption, distribution, metabolism, excretion, and toxicity (ADMET). The SDF-format structure of each compound was submitted through the prediction window under the ADME and Toxicity tabs. Predictions such as human intestinal absorption (HIA), blood–brain barrier permeability, and mutagenicity were generated. This early-stage screening was essential for identifying compounds with favorable pharmacokinetic profiles and low toxicity [15].

2.3.3. Pharmacophore Screening

Pharmacophore screening was performed using LigandScout. An active and decoy dataset was retrieved from the DUD-E database (https://dude.docking.org/targets), along with a dataset of 20 test compounds. The active and decoy files were imported into the Ligand-Based Perspective of LigandScout. Ten pharmacophore models were generated and saved in .pmz format, representing essential interaction features, including hydrogen-bond acceptors/donors, aromatic rings, and hydrophobic regions relevant to VEGFR-2 inhibition.

The resulting pharmacophore models were screened against the decoy and test compound datasets using the "screening perspective" feature in LigandScout. Receiver Operating Characteristic (ROC) curve analysis was employed to assess model performance and determine the optimal predictive model. The validated models were then used to screen test compounds from *Cinnamomum burmannii*. Compounds matching the key interaction features were identified as "hits" and selected for subsequent molecular docking analysis. This virtual screening approach enabled efficient selection of potential VEGFR-2 inhibitors from a large pool of natural compounds [16].

2.3.4. Molecular Docking Simulation

All 20 test compounds, together with the native ligand and apatinib as a reference inhibitor, were subjected to molecular docking against VEGFR-2 (PDB ID: 2P2I); two-dimensional and three-dimensional interaction maps were subsequently generated for the compounds identified as hits in pharmacophore screening. The protein structure was downloaded from the Protein Data Bank (https://www.rcsb.org/), and standard ligands were removed using BIOVIA Discovery Studio to prepare the receptor. Polar hydrogens and Kollman charges were added using AutoDock 4.2.6, and the receptor was saved in .pdbqt format for docking. Geometry optimization of the ligands was performed using Chem3D Pro 12.0 with molecular mechanics (MM2) calculations. SMILES codes of the test compounds were retrieved from PubChem and converted to 3D structures. Optimization was performed by minimizing the energy until the RMS gradient reached 0.010. The ligands were then prepared in AutoDock 4.2.6 by adding Gasteiger charges, hydrogen atoms, and defining rotatable bonds. A grid box was configured with dimensions of 40 × 48 × 40 grid points, centered at (x = 37.585, y = 35.805, z = 11.964), with a spacing of 0.375 Å. The docking parameters were set using the Lamarckian Genetic Algorithm with 100 runs. Grid parameter files (.gpf) and docking parameter files (.dpf) were created and saved. Docking simulations were executed from the Windows command line, and the resulting output files were analyzed for ligand-receptor interactions [17]. Visualization of 2D and 3D interactions between the ligands and VEGFR-2 was performed using BIOVIA Discovery Studio 2025.

3. RESULTS AND DISCUSSION

This section presents the results of the physicochemical, pharmacokinetic, pharmacophore, and molecular docking evaluations of the bioactive compounds from *Cinnamomum burmannii* as candidate VEGFR-2 inhibitors, followed by a discussion of their implications for anticancer drug development.

3.1. Lipinski's Rule of Five Prediction

Lipinski's rule of five (RO5) analysis was conducted to evaluate the physicochemical properties of the test compounds and assess their potential as orally active drugs. The parameters assessed included a molecular weight of less than 500 Da, a logP value of less than 5, no more than 5 hydrogen-bond donors, and no more than 10 hydrogen-bond acceptors, with a maximum of 2 violations allowed. Among the 20 compounds derived from *C. burmannii*, 19 fulfilled the RO5 criteria, indicating favorable drug-likeness profiles for oral administration. These compounds demonstrated suitable molecular weights, lipophilicity, and hydrogen bonding characteristics, suggesting good membrane permeability and potential for oral bioavailability. Only one compound, procyanidin A1, failed to meet the RO5 requirements. This compound had a molecular weight of 594.52 Da, exceeded the hydrogen-bond donor limit with 10 donors, and had 13 hydrogen-bond acceptors, violating three RO5 criteria. These properties suggest that procyanidin A1 may have poor oral bioavailability and reduced membrane permeability compared to the other compounds. Overall, the results indicate that most of the tested compounds possess promising physicochemical characteristics for development as orally administered drug candidates (Table 1).

Table 1. Lipinski's rule of five prediction results of Cinnamomum burmannii

Compound Name	**Molecular Weight (< 500 Da)**	**LogP (< 5)**	**H-bond Donor (≤ 5)**	**H-bond Acceptor (≤ 10)**	**Conclusion**
Cinnamyl alcohol	134.17	1.69	1	1	0 (passed)
Coumarin	146.14	1.79	0	2	0 (passed)
Cinnamic acid	148.16	1.78	1	2	0 (passed)
Cinnamaldehyde	132.16	1.90	0	1	0 (passed)
Anthocyanin	207.25	4.38	1	0	0 (passed)
Eugenol	164.20	2.13	1	2	0 (passed)
Beta-Caryophyllene	204.35	4.73	0	0	0 (passed)
Caryophyllene oxide	220.35	3.94	0	1	0 (passed)
Cinnamyl acetate	176.21	2.26	0	2	0 (passed)
Copaene	204.35	4.27	0	0	0 (passed)
Linoleic acid	280.44	5.88	1	2	0 (passed)
Methyl hydroxychalcone	238.28	3.60	1	2	0 (passed)
Melanin	318.28	1.33	2	6	0 (passed)
Eucalyptol	154.25	2.74	0	1	0 (passed)
Muurolene	204.35	4.58	0	0	0 (passed)
4-Terpineol	154.25	2.50	1	1	0 (passed)
Procyanidin A1	594.52	2.73	10	13	3 (not passed)
Endo-Borneol	154.25	2.19	1	1	0 (passed)
Alpha-Terpineol	154.25	2.50	1	1	0 (passed)
Cadina-1(10),4-diene	204.35	4.73	0	0	0 (passed)

3.2. ADMET Prediction

ADMET predictions were conducted to evaluate the pharmacokinetic behavior and toxicity profiles of the test compounds, providing insight into their safety and suitability as drug candidates. First, absorption was evaluated using human intestinal absorption (HIA) and Caco-2 permeability predictions. HIA results indicated that 19 out of 20 compounds exhibited high absorption rates (95.9–100%), suggesting excellent potential for intestinal uptake. Only one compound, procyanidin A1, showed poor intestinal absorption, with an HIA value of 16.11%. Caco-2 permeability results showed that alpha-terpineol had high permeability (>70), while the remaining compounds fell within the medium range (8.64–56.34 nm/sec), indicating moderate intestinal epithelial cell absorption. The distribution parameter was evaluated through blood-brain barrier (BBB) permeability and plasma protein binding (PPB). Thirteen compounds exhibited high plasma protein-binding affinity (>90%), which may influence their bioavailability and distribution. The BBB predictions revealed that 12 compounds had high permeability (BBB > 2), 6 compounds had moderate permeability (BBB 0.1–2), and 2 compounds showed low BBB penetration (<0.1) (Table 2). For non-CNS-targeting drugs, lower BBB permeability is generally preferred, making the low-penetrating compounds more favorable in this context.

Table 2. ADMET results of Cinnamomum burmannii bioactive compounds

Compound Name	**HIA (%)**	**Caco-2 (nm/sec)**	**PPB (%)**	**BBB**	**Mutagen**	**Carcinogen (Mouse)**	**Carcinogen (Rat)**
Cinnamyl alcohol	100.00	22.06	40.56	1.71	Mutagen	–	–
Coumarin	100.00	32.12	43.40	1.60	Mutagen	+	+
Cinnamic acid	97.85	21.03	60.85	1.86	Mutagen	–	–
Cinnamaldehyde	100.00	23.78	52.90	1.26	Mutagen	–	–
Anthocyanin	100.00	28.09	100.00	2.72	Mutagen	–	–
Eugenol	96.78	46.89	100.00	2.26	Mutagen	+	+
Beta-caryophyllene	100.00	23.63	100.00	13.31	Mutagen	–	+
Caryophyllene oxide	100.00	56.34	90.84	3.75	Mutagen	+	+
Cinnamyl acetate	100.00	43.07	70.70	1.50	Mutagen	–	–
Copaene	100.00	23.63	100.00	11.14	Non-mutagen	–	+
Linoleic acid	98.37	28.08	100.00	7.32	Mutagen	+	+
Methylhydroxychalcone	95.92	27.30	92.47	2.93	Mutagen	–	–
Melanin	96.08	21.08	41.82	0.06	Mutagen	–	+
Eucalyptol	100.00	21.90	100.00	1.47	Mutagen	+	+
Muurolene	100.00	23.63	100.00	13.29	Mutagen	+	+
4-terpineol	100.00	50.81	100.00	5.54	Mutagen	+	–
Procyanidin A1	16.11	8.64	100.00	0.07	Non-mutagen	–	+
Endo-borneol	100.00	24.23	100.00	3.80	Mutagen	–	+
Alpha-terpineol	100.00	322.76	23.42	5.12	Mutagen	–	–
Cadina-1(10),4-diene	100.00	23.64	100.00	13.93	Mutagen	+	+

Mutagen/carcinogen columns: "+" = positive prediction (mutagenic/carcinogenic), "–" = negative prediction. HIA = human intestinal absorption; Caco-2 = Caco-2 cell permeability; PPB = plasma protein binding; BBB = blood–brain barrier permeability.

Toxicity analysis revealed that only 2 of the 20 compounds were predicted to be non-mutagenic. In contrast, the remaining compounds posed a risk of inducing genetic mutations, underscoring the need for further validation. Regarding carcinogenicity, 12 compounds were predicted to be non-carcinogenic in mice and 8 in rats. Among all compounds, copaene and procyanidin A1 demonstrated the most favorable toxicity profiles, being both non-mutagenic and non-carcinogenic in mice. Overall, most of the tested compounds showed good intestinal absorption and moderate permeability with acceptable distribution profiles, but the predicted mutagenicity of 18 of the 20 compounds is a substantive concern that cannot be resolved computationally. Copaene and procyanidin A1 therefore presented the most favorable predicted safety profiles among the compounds tested.

3.3. Pharmacophore Screening

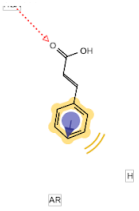
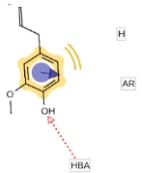
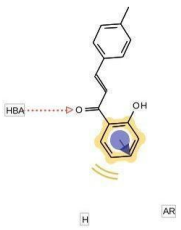
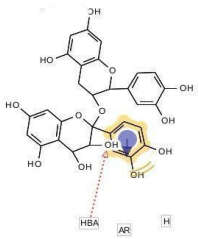
Pharmacophore screening was conducted to evaluate the potential of bioactive compounds from *C. burmannii* as inhibitors of VEGFR-2, a receptor tyrosine kinase crucial in angiogenesis and cancer cell proliferation. A total of 20 test compounds were evaluated using LigandScout, reusing ligand data from the DUD-E database, which provides validated sets of active ligands and decoy molecules for pharmacophore modeling. Ten pharmacophore models were successfully generated based on a training set of 100 active and 400 decoy compounds. These models were then validated using ROC curve analysis. A model was considered valid if the area under the curve (AUC) exceeded 0.70 (Table 3). All generated models met this criterion. Models 1–3 achieved the highest AUC value (0.75); model 3 was selected for subsequent screening because it retrieved the largest number of hits at an equivalent true-positive count, indicating acceptable discrimination between active and inactive compounds.

Table 3. Pharmacophore screening validation results

Pharmacophore Model	Hits	True Positive	False Positive	AUC
1	295	90	205	0.75
2	295	90	205	0.75
3	299	90	209	0.75
4	290	87	203	0.74
5	291	87	204	0.74
6	294	88	206	0.73
7	295	88	207	0.73
8	294	87	207	0.73
9	297	88	209	0.72
10	301	88	213	0.71

This top-performing model yielded 299 hit compounds, comprising 90 true positives and 209 false positives, demonstrating its effectiveness in identifying active VEGFR-2 inhibitors. Among the screened C. burmannii compounds, six were identified as hits based on their alignment with key pharmacophore features of the VEGFR-2 active site. Of these, procyanidin A1 achieved the highest fit score (38.27), followed by methylhydroxychalcone (37.99) and eugenol (37.03), suggesting strong potential for binding to VEGFR-2. The high fit scores and favorable alignment with critical pharmacophore features support the potential of these compounds as antiangiogenic agents targeting VEGFR-2 (Table 4).

Table 4. Pharmacophore fit score of hit compounds

Hit Compound	Fit Score	Visualization
Cinnamic acid	35.72	
Cinnamaldehyde	35.79	
Cinnamyl alcohol	35.87	
Eugenol	37.03	
Methylhydroxychalcone	37.99	
Procyanidin A1	38.27	

3.4. Molecular Docking Simulation

Molecular docking simulations were conducted following validation of the docking protocol to identify the active binding site of VEGFR-2 and determine the optimal grid box parameters for accurate prediction of ligand-receptor interactions [18]. The docking protocol was validated by redocking the native ligand into the VEGFR-2 binding pocket, yielding an

RMSD value of 0.64 Å. An RMSD ≤ 2 Å indicates high reliability and accuracy of the docking method. Therefore, the validation results confirmed that the docking procedure used in this study was appropriate.

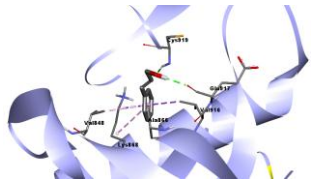
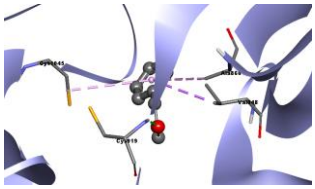
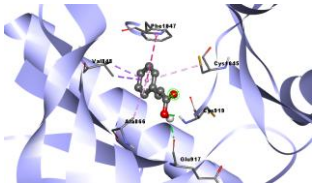
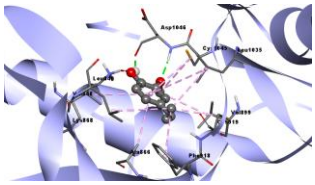
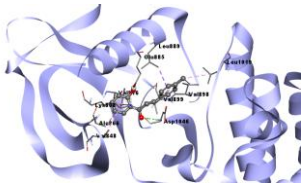
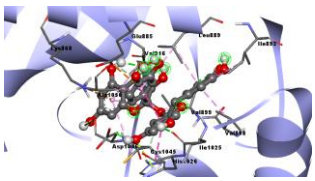
Docking simulations of 20 bioactive compounds from *C. burmannii* against VEGFR-2 were then performed to evaluate their binding conformations, binding affinities, and inhibition constants. The results showed that several compounds formed stable interactions with key residues in the VEGFR-2 active site, including Val916, Val848, Ala866, Cys1045, Lys868, Phe1047, and Val899 (Table 5). Importantly, both the native ligand and the reference inhibitor apatinib formed conventional hydrogen bonds with Asp1046, a critical residue in VEGFR-2-ligand interactions. Among the test compounds, copaene returned the lowest binding energy (−8.58 kcal/mol), closely followed by methylhydroxychalcone (−8.51 kcal/mol; Ki = 579.80 nM). Copaene, however, formed no hydrogen bonds with the receptor, whereas methylhydroxychalcone combined an essentially equivalent binding energy with conventional hydrogen bonding to Asp1046, indicating a more specific interaction with the VEGFR-2 active site. Overall, conventional hydrogen bonding with Asp1046 — the key contact formed by both the native ligand and apatinib — was observed for coumarin, eugenol, eucalyptol, 4-terpineol, endo-borneol, alpha-terpineol, procyanidin A1, and methylhydroxychalcone (Table 5). Among these, methylhydroxychalcone combined that interaction with the most favorable binding energy and the broadest set of hydrophobic contacts, highlighting its promise as a candidate antiangiogenic agent targeting VEGFR-2. Eugenol also engaged Asp1046, although an unfavorable donor–donor contact with Lys868 was detected in the same pose, while procyanidin A1 returned a positive binding energy (+6.68 kcal/mol), indicating that no energetically favorable pose was obtained despite its high pharmacophore fit score. The two- and three-dimensional interaction maps of the six compounds identified as pharmacophore hits are presented in Table 6.

Table 5. Molecular docking results for *C. burmannii* bioactive compounds on VEGFR-2

Compound	**Binding Energy (kcal/mol)**	**Ki**	**Hydrogen Bonding**	**Other Interactions**
Native ligand	-11.78	2.31 nM	Cys A:919; Asp A:1046; Glu A:917 (Carbon H-Bond)	Pi-Sigma: Leu A:1035, Phe A:1047, Leu A:1019; Pi-Alkyl: Glu A:885, Leu A:840, Ala A:866, Leu A:889, Val A:889, Cys A:1045, Cys A:1024
Apatinib (reference)	-9.91	54.31 nM	Asp A:1046	Pi-Sigma: Leu A:889; Pi-Sulfur: Cys A:1045; Alkyl & Pi-Alkyl: Ala A:866, Val A:848, Leu A:1035, Ala A:1050
Cinnamyl alcohol	-5.36	118.13 μM	Glu A:917; Cys A:919	Pi-Sigma: Lys A:868, Val A:916; Pi-Alkyl: Val A:848, Ala A:866
Coumarin	-6.04	37.41 μM	Asp A:1046; Lys A:868	Pi-Sigma: Val A:916; Pi-Sulfur: Cys A:1045; Pi-Alkyl: Ala A:866, Val A:848, Val A:914
Cinnamic acid	-5.54	86.94 μM	Glu A:917; Cys A:919	Pi-Sigma: VAL A:848; Pi-Pi T-Shaped: PHE A:1047; Pi-Alkyl: ALA A:866, CYS A:1045
Cinnamaldehyde	-5.34	122.62 μM	Cys A:919	Pi-Sigma: Val A:848; Pi-Alkyl: Cys A:1045, Ala A:866
Anthocyanin	-7.31	4.41 μM	-	Pi-Sigma: Val A:916; Pi-Cation & Pi-Anion: Glu A:885, Lys A:868; Alkyl & Pi-Alkyl: Ala A:866, Val A:848, Val A:899, Leu A:889, Cys A:1045
Eugenol	-5.71	64.70 μM	Asp A:1046 (Unfavorable Donor-Donor: Lys A:868)	Alkyl & Pi-Alkyl: Val A:899, Val A:848, Ala A:866, Leu A:840, Leu A:1035, Cys A:1045, Cys A:919, Phe A:918

Beta-caryophyllene	-8.13	1.10 μM	-	Pi-Sigma: Phe A:1047; Pi-Alkyl: Val A:899, Val A:916, Val A:848, Val A:914, Ala A:866, Lys A:868, Cys A:1045
Caryophyllene oxide	-8.07	1.22 μM	-	Alkyl & Pi-Alkyl: Ala A:866, Cys A:1045, Lys A:868, Phe A:1047, Val A:916, Val A:848, Val A:914, Leu A:1035
Cinnamyl acetate	-6.45	18.57 μM	Cys A:919	Pi-Sigma: Val A:916; Alkyl & Pi-Alkyl: Lys A:868, Phe A:1047, Val A:848, Ala A:866
Copaene	-8.58	516.95 nM	-	Alkyl & Pi-Alkyl: Val A:848, Val A:916, Val A:899, Ala A:866, Cys A:1045, Phe A:1047, Leu A:1035, Leu A:840, Lys A:868
Linoleic acid	-6.80	10.33 μM	Cys A:919	Alkyl & Pi-Alkyl: His A:1026, Leu A:889, Lys A:868, Val A:899, Val A:914, Val A:916, Val A:848, Cys A:1045, Ala A:866
Methylhydroxychalcone	-8.51	579.80 nM	Asp A:1046; Glu A:885	Pi-Cation: Lys A:868; Pi-Sigma: Leu A:889, Val A:916; Alkyl & Pi-Alkyl: Val A:916, Val A:899, Val A:848, Lys A:868, Ala A:866, Cys A:1045, Leu A:840, Phe A:1047
Melanin	-7.90	1.62 μM	Lys A:868; Ile A:1044 (Carbon H-Bond: Asp A:1046)	Pi-Cation: His A:1026; Alkyl & Pi-Alkyl: Leu A:1019, Cys A:1045, Leu A:889, Val A:899, Val A:916
Eucalyptol	-6.20	28.56 μM	Asp A:1046	Alkyl & Pi-Alkyl: Val A:916, Val A:848, Val A:899, Phe A:1047, Cys A:1045, Ala A:866, Lys A:868, Leu A:1035
Muurolene	-8.06	1.24 μM	-	Alkyl & Pi-Alkyl: Val A:916, Val A:899, Lys A:868, Ala A:866, Cys A:1045, Val A:848, Phe A:1047, Leu A:840
4-terpineol	-5.97	42.37 μM	Asp A:1046 (Carbon H-Bond: Lys A:868)	Pi-Alkyl & Alkyl: Cys A:1045, Val A:848, Val A:916, Val A:914, Ala A:866
Procyanidin A1	+6.68	Unavailable	Asp A:1046; Val A:899; Ile A:1025 (Carbon H-Bond: Cys A:1045, Glu A:885)	Pi-Alkyl: Val A:916, Val A:898, Ile A:892, Leu A:889, Ala A:1050; Pi-Cation & Pi-Anion: Lys A:868; Pi-Lone Pair: His A:1026; Pi-Pi Stacked
Endo-borneol	-6.14	31.51 μM	Asp A:1046	Alkyl & Pi-Alkyl: Ala A:866, Val A:916, Leu A:840, Leu A:1035, Val A:899, Cys A:1045, Val A:848; Pi-Sigma: Phe A:1047
Alpha-terpineol	-6.19	28.91 μM	Asp A:1046	Pi-Sigma: Phe A:1047; Alkyl & Pi-Alkyl: Phe A:918, Leu A:840, Leu A:1035, Cys A:919, Cys A:1045, Ala A:866, Val A:848, Val A:916
Cadina-1(10),4-diene	-8.20	973.84 nM	-	Pi-Sigma: Phe A:1047; Alkyl: Val A:889, Val A:848, Val A:914, Val A:916, Ala A:866, Leu A:1035, Lys A:868, Cys A:1045

Table 6. Molecular docking visualization of hit compounds

Compound	3D Visualization
Cinnamyl alcohol	
Cinnamaldehyde	
Cinnamic acid	
Eugenol	
Methylhydroxychalcone	
Procyanidin A1	

3.5. Discussion

In silico approaches offer a cost-effective and time-efficient strategy for early-stage drug discovery, particularly in identifying novel inhibitors against validated molecular targets such as VEGFR-2. These methods enable the rapid prediction of drug-like characteristics, including target interaction, pharmacokinetics, and toxicity profiles, thereby reducing the need for extensive wet-lab screening [19]. In this study, multiple in silico analyses, including Lipinski's RO5, ADMET prediction, pharmacophore modeling, and molecular docking, were employed to assess the potential of bioactive compounds from *C. burmannii* as VEGFR-2 inhibitors, a receptor tyrosine kinase implicated in tumor angiogenesis and progression. Physicochemical screening via RO5 revealed that most of the compounds tested (19 of 20) were suitable for oral formulation, with acceptable molecular weights, lipophilicities, and hydrogen-bonding parameters. Although procyanidin A1 did not meet RO5 due to its dimeric structure and high polarity, its metabolites formed via enzymatic breakdown in the gut can still exert bioactive effects systemically, suggesting that pharmacological activity cannot be ruled out solely based on size or polarity [20,21]. Further screening using ADMET predictions identified several compounds with favorable

pharmacokinetic properties. Cinnamyl acetate, for instance, exhibited good absorption, moderate permeability, and an acceptable distribution profile, yet was predicted to be mutagenic — a pattern shared by most of the library and one that underlines the importance of early safety profiling.

Pharmacophore modeling played a crucial role in prioritizing compounds with structural and functional similarities to known VEGFR-2 ligands. Among the 10 validated models, model 3 retrieved the largest number of actives at the highest AUC obtained (0.75), a moderate but acceptable level of enrichment for screening natural-product libraries [22]. Six hit compounds were identified with favorable pharmacophore alignment, indicating likely VEGFR-2 inhibition. Notably, methylhydroxychalcone emerged as a top candidate from both pharmacophore and molecular docking analysis. It displayed strong interactions with critical residues (e.g., ASP A:1046), a low binding energy (−8.51 kcal/mol), and an inhibition constant of 579.8 nM. These findings are supported by prior studies showing that chalcone derivatives can effectively inhibit receptor tyrosine kinases, including VEGFR-2 and HER2 [23]. Furthermore, methylhydroxychalcone has demonstrated antiproliferative activity in vitro. A previous study reported that the structurally related methoxychalcone induced cell-cycle arrest and apoptosis in hormone-resistant prostate cancer cells through PI3K-independent inhibition of the mTOR pathway [25]. Metochalcone, another related chalcone, has likewise been reported to induce a senescence-associated secretory phenotype via the JAK2/STAT3 pathway in breast cancer cells [26]. Pharmacokinetic analysis also supported the potential of methylhydroxychalcone for oral administration, with excellent intestinal absorption, high plasma protein binding, and moderate Caco-2 permeability. However, the predicted BBB value of 2.93 places methylhydroxychalcone in the high-penetration class, which is undesirable for a non-CNS target and may increase the risk of central off-target effects. Binding affinity and safety are independent properties, and a favorable docking score does not offset an unfavorable predicted toxicity profile; both must therefore be weighed before the compound is advanced.

A balanced reading of the predicted safety data is warranted before methylhydroxychalcone is described as a viable lead. Of the 20 compounds examined, 18 were flagged as mutagenic, and only 12 and 8 were predicted to be non-carcinogenic in mice and rats, respectively; methylhydroxychalcone itself was predicted to be mutagenic, although non-carcinogenic in both species. Its high plasma protein binding (92.47%) would further restrict the free fraction available to reach the receptor, and the high predicted blood–brain barrier penetration compounds the concern over central exposure. Copaene and procyanidin A1 were the only compounds predicted to be non-mutagenic, yet neither is a realistic alternative: copaene formed no hydrogen bonds with the active site, while procyanidin A1 violated three RO5 criteria, showed poor intestinal absorption (HIA 16.11%) and returned a positive binding energy. It should also be emphasised that these values are structure-based predictions from a single platform (PreADMET), which carry appreciable false-positive rates for bacterial mutagenicity and are not a substitute for measurement. Experimental confirmation is therefore required before any claim of preclinical safety can be made — specifically an Ames test to resolve the mutagenicity prediction, a micronucleus or chromosomal aberration assay, cytotoxicity testing against non-malignant colon epithelial cells to establish a selectivity index relative to colon cancer lines, and a VEGFR-2 kinase inhibition assay to confirm that the predicted binding translates into target engagement. Until those data are available, methylhydroxychalcone is best regarded as a computational hit requiring experimental validation rather than a safety-qualified lead compound.

4. CONCLUSION

Taken together, these findings indicate that methylhydroxychalcone from *C. burmannii* represents a promising computational hit for VEGFR-2-targeted therapy. The use of an integrated computational strategy that combines drug-likeness assessment, ADMET prediction, pharmacophore modeling, and molecular docking provides a comprehensive and efficient framework for evaluating the efficacy and safety profiles of candidate compounds at an early stage of drug discovery. This multi-layered *in silico* approach not only strengthened confidence in the predicted VEGFR-2 interactions but also enabled the early identification of potential pharmacokinetic and toxicity concerns, thereby reducing reliance on costly and time-consuming experimental screening. Nevertheless, the predicted mutagenicity and high blood–brain barrier penetration of methylhydroxychalcone are material limitations rather than minor caveats, and experimental validation, including Ames testing, cytotoxicity screening against non-malignant colon epithelium, and a VEGFR-2 kinase inhibition assay is required before the compound can be regarded as a safety-qualified lead.

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