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PREDICTION OF ANTIFUNGAL ACTIVITY AND PHARMACOKINETIC PROPERTIES OF *Alpinia galanga* SECONDARY METABOLITES USING PASS Online, SwissADME, AND pkCSM

PREDIKSI AKTIVITAS ANTIJAMUR DAN SIFAT FARMAKOKINETIK METABOLIT SEKUNDER *Alpinia galanga* MENGGUNAKAN PASS Online, SwissADME, DAN pkCSM

Muliani[1*], Mohammad Ramdani [1], Baiq Hairunnisa Permatasari [1], Gita Olipia[1], Evandi Gunawan[1], Frendy Ferdian [1], Muhammad Rafli Habibi Hasri [1], Dodi Iskandar [2]

[1]Plantation Crop Cultivation, Department of Agricultural Technology, Pontianak State Polytechnic
[2]Integrated Plantation Product Processing, Department of Agricultural Technology, Pontianak State Polytechnic

* Correspondent Email: salamahmul@gmail.com

Abstract

Galangal (*Alpinia galanga*) is a medicinal plant in the family Zingiberaceae known for various biological activities, including natural antifungal properties. This study aimed to analyze the potential of galangal secondary metabolites as natural-product-based antifungal candidates using an *in silico* approach. The analysis was conducted using several bioinformatics platforms, including PASS Online for antifungal activity prediction, SwissADME for physicochemical properties, water solubility, bioavailability, and drug-likeness, and pkCSM for toxicity prediction. The results showed that most galangal secondary metabolites exhibited considerable antifungal activity, as indicated by their probability of activity (Pa) values. Alpha-farnesene demonstrated the highest Pa value, followed by 1'-acetoxyeugenol acetate, galanal A, galanal B, galanganol A, and galanganol B. These compounds are known to act through mechanisms involving disruption of cell membrane permeability, inhibition of metabolism, and damage to fungal cell structures. Physicochemical property analysis indicated that the majority of compounds had molecular weights below 500, topological polar surface area (TPSA) values below 140, and a bioavailability score of 0.55, suggesting good oral absorption potential. Drug-likeness analysis revealed that most compounds complied with Lipinski, Veber, Egan, Ghose, and Muegge rules, indicating their potential for development as natural drug candidates. Furthermore, toxicity predictions indicated that most compounds were non-hepatotoxic and non-mutagenic, although several phenolic compounds exhibited mild potential for toxicity at certain concentrations. Overall, the *in silico* analysis indicated that galangal secondary metabolites have significant potential as effective, relatively safe, natural product-based antifungal candidates. However, further studies through *in vitro* and *in vivo* testing are still required to validate the biological effectiveness and safety of these compounds.

Keywords: *Alpinia galanga, antifungal, in silico, secondary metabolites, SwissADME*

Abstrak

Tanaman lengkuas (*Alpinia galanga*) merupakan salah satu tanaman obat dari famili Zingiberaceae yang diketahui memiliki berbagai aktivitas biologis, termasuk sebagai agen antifungi alami. Penelitian ini bertujuan untuk menganalisis potensi metabolit sekunder lengkuas sebagai kandidat antifungi berbasis bahan alam melalui pendekatan in silico. Analisis dilakukan menggunakan beberapa platform bioinformatika, meliputi PASS Online untuk prediksi aktivitas antifungi, SwissADME untuk analisis properti fisikokimia, solubility, bioavailability, dan drug-likeness, serta pkCSM untuk prediksi toksisitas senyawa. Hasil penelitian menunjukkan bahwa sebagian besar metabolit sekunder lengkuas memiliki

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aktivitas antifungi yang cukup baik berdasarkan nilai probability of activity (Pa). Senyawa alpha-farnesene menunjukkan nilai Pa tertinggi, diikuti oleh 1'-acetoxyeugenol acetate, galanal A, galanal B, galanganol A, dan galanganol B. Senyawa-senyawa tersebut diketahui bekerja melalui mekanisme gangguan permeabilitas membran sel, penghambatan metabolisme, serta kerusakan struktur sel fungi. Analisis physicochemical properties menunjukkan bahwa mayoritas senyawa memiliki berat molekul di bawah 500 , nilai topological polar surface area (TPSA) di bawah 140 , serta bioavailability score sebesar 0.55 yang mengindikasikan kemampuan absorpsi oral yang baik. Hasil drug-likeness menunjukkan bahwa sebagian besar senyawa memenuhi aturan Lipinski, Veber, Egan, Ghose, dan Muegge, sehingga berpotensi dikembangkan sebagai kandidat obat alami. Selain itu, prediksi toksisitas menunjukkan bahwa mayoritas senyawa tidak bersifat hepatotoksik maupun mutagenik, meskipun beberapa senyawa fenolik menunjukkan potensi toksisitas ringan pada konsentrasi tertentu. Secara keseluruhan, hasil analisis in silico menunjukkan bahwa metabolit sekunder lengkuas berpotensi besar sebagai kandidat antifungi berbasis bahan alam yang efektif dan relatif aman. Namun, penelitian lanjutan melalui uji in vitro dan in vivo tetap diperlukan untuk memvalidasi efektivitas dan keamanan senyawa secara biologis.

Kata kunci: *Alpinia galanga*, antifungi, in silico, metabolit sekunder, SwissADME

INTRODUCTION

Fungal infections are among the growing health and agricultural problems in many countries. Pathogenic fungi can cause various diseases in humans, animals, and plants, thereby affecting health and food production and causing economic losses. The continuous use of synthetic antifungal agents is known to create several problems, including microbial resistance, environmental chemical residues, and toxic effects on non-target organisms. Fungal resistance to antifungal drugs has become a serious challenge because it can reduce therapeutic effectiveness and increase the risk of treatment failure. In addition, the use of synthetic fungicides in the agricultural sector is frequently associated with environmental pollution and ecosystem disruption. Therefore, the development of safer, more effective, and environmentally friendly antifungal alternatives is needed, one of which is through the utilization of bioactive compounds derived from medicinal plants (Alsalih, 2025).

Medicinal plants have long been used in traditional medicine because they contain a variety of secondary metabolites with high biological activity. Secondary metabolites such as flavonoids, terpenoids, alkaloids, phenolics, and essential oils are known to exhibit antimicrobial, antioxidant, anti-inflammatory, and antifungal activities. Compared to synthetic antifungal agents, natural compounds from plants tend to have fewer side effects and are more easily degraded in the environment, making them safer for long-term use. In recent years, research on the utilization of herbal plants as natural antifungal sources has continued to grow in line with the increasing demand for safer and more sustainable natural product-based materials (Merino-Ramirez & Salvador-Reyes, 2026).

One medicinal plant with considerable potential as a natural antifungal agent is galangal (*Alpinia galanga*). This plant, belonging to the Zingiberaceae family, is widely used as both a spice and traditional medicine in many Asian countries, including Indonesia. Empirically, galangal has been used to treat digestive disorders, infections, inflammation, and various skin diseases. The pharmacological potential of galangal is closely linked to its diverse array of

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secondary metabolites, particularly flavonoids, phenolics, monoterpenes, sesquiterpenes, and diterpenoids. Various studies have reported that galangal extracts and essential oils possess antibacterial, antioxidant, anticancer, anti-inflammatory, and antifungal activities against a wide range of pathogenic microorganisms (Aziz *et al*., 2024).

Galangal essential oil contains various volatile compounds, including alpha-farnesene, beta-pinene, alpha-pinene, alpha-caryophyllene, eugenol, and 4-terpineol, which exhibit considerable antimicrobial activity. Terpenoid compounds are known to inhibit fungal growth by disrupting cell membrane permeability. The hydrophobic nature of terpenoids enables direct interaction with the lipid bilayer of microbial membranes, leading to ion leakage, organelle damage, and disruption of cellular metabolism. In addition, several sesquiterpene compounds are known to inhibit biofilm formation and mycelial growth in pathogenic fungi. These biological activities make galangal essential oil highly promising as a source of natural antifungal agents in both health and agricultural applications (Destryana *et al*., 2024).

In addition to terpenoid compounds, galangal is rich in flavonoids and phenolics, including galangin, galanganol, trans-*p*-hydroxycinnamaldehyde, and eugenol. Flavonoids are known to exhibit broad biological activity by inhibiting cell wall synthesis, disrupting energy metabolism, and increasing oxidative stress in microorganisms. The presence of hydroxyl groups in flavonoids enables them to form hydrogen bonds with target proteins and enzymes, thereby enhancing antifungal and antibacterial activities. Eugenol, a major component of galangal essential oil, is also known for its ability to damage plasma membranes and increase microbial cell permeability. Recent studies have shown that combinations of flavonoid and phenolic compounds in herbal plants can produce synergistic effects in inhibiting the growth of pathogenic fungi, making them potential safer alternatives to synthetic fungicides (Cho *et al*., 2026).

The development of bioinformatics and computational chemistry technologies now enables the rapid identification of compounds' biological potential through *in silico* approaches. *In silico* methods have become increasingly important in natural product research because they can accelerate initial drug-candidate screening at a lower cost than conventional experimental methods. *In silico* analysis can be used to predict biological activity, pharmacokinetic properties, bioavailability, drug-likeness, and compound toxicity before further laboratory testing. This approach assists researchers in selecting the most promising candidate compounds, thereby making the research process more efficient and targeted (Fu & Chen, 2025).

One of the most widely used platforms for biological activity prediction is PASS Online (Prediction of Activity Spectra for Substances). PASS Online predicts the potential biological activity of a compound based on its structural similarity to previously identified active compounds. Prediction results are expressed as probability of activity (Pa), where values closer to 1 indicate a higher probability of biological activity. This method is widely used in the preliminary screening of natural compounds because it provides relatively good accuracy in estimating molecular pharmacological activity. In natural product research, PASS Online is particularly useful for identifying antifungal candidate compounds prior to direct biological testing (Gómez-Gaviria *et al*., 2025).

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In addition to biological activity, the pharmacokinetic characteristics of a compound are important factors in drug candidate development. A good active compound must not only possess high biological activity but also be capable of being properly absorbed, distributed, metabolized, and excreted within the body. Therefore, the analysis of water solubility, lipophilicity, bioavailability score, and physicochemical properties becomes highly important. Parameters such as molecular weight, topological polar surface area (TPSA), hydrogen-bond donor and acceptor counts, and fraction Csp3 are known to influence biological permeability and oral absorption strongly. According to recent studies, compounds with molecular weights below 500 and TPSA values below 140 generally exhibit better oral absorption capabilities, making them promising candidates for natural product-based drugs (Khibech *et al*., 2026).

SwissADME is one of the most widely used bioinformatics platforms for analyzing the pharmacokinetic characteristics and drug-likeness of natural compounds. SwissADME can predict physicochemical properties, solubility, lipophilicity, and bioavailability, as well as compliance with various drug-likeness rules, including the Lipinski, Veber, Ghose, Egan, and Muegge rules. These rules are used to estimate oral absorption capability and biological permeability of compounds. Compounds that fulfill drug-likeness parameters generally have a greater chance of being developed as drug candidates because they possess good molecular stability and favorable pharmacokinetic characteristics (Shuvo *et al*., 2025).

In addition to biological effectiveness and pharmacokinetic characteristics, safety is an important factor in the development of natural drug candidates. Compounds with high biological activity are not necessarily safe if they are toxic to humans or the environment. Therefore, toxicity analysis is an important stage in natural product research. The *in silico* approach using the pkCSM platform can be utilized to predict hepatotoxicity, AMES toxicity, and environmental toxicity of compounds. Computational toxicity prediction is widely used because it can provide an initial overview of a compound's biological safety before laboratory testing. This method is considered more efficient, cost-effective, and capable of accelerating the selection process of safe and effective candidate compounds (Lopes *et al*., 2026).

Based on various previous studies, secondary metabolites in galangal have demonstrated excellent biological potential as natural antifungal agents. However, information on the relationships among antifungal activity, pharmacokinetic characteristics, drug-likeness, physicochemical properties, and toxicity of galangal active compounds still requires further investigation using an integrated *in silico* approach. Therefore, this study was conducted to analyze the potential of secondary metabolites from galangal (*Alpinia galanga*) as natural-product-based antifungal candidates using PASS Online, SwissADME, and pkCSM. The results of this study are expected to provide scientific information regarding the biological potential, pharmacokinetic characteristics, and safety of galangal secondary metabolites, thereby serving as a basis for the development of safer, more effective, and environmentally friendly natural antifungal agents.

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RESEARCH METHODS

This descriptive study employed an in silico approach to assess the potential of secondary metabolites from galangal (*Alpinia galanga*) as natural-product-based antifungal candidates. The *in silico* approach was employed because it can rapidly, efficiently, and cost-effectively provide preliminary information on the biological activity, physicochemical characteristics, pharmacokinetics, drug-likeness, and toxicity of compounds before direct experimental testing. *In silico* analysis is widely used in natural product research because it can assist in the preliminary screening of bioactive compounds with potential as drugs or natural biofungicides.

The research was conducted through several stages: identification of galangal secondary metabolites; collection of compound chemical structures; antifungal activity analysis using PASS Online; physicochemical properties and drug-likeness analysis using SwissADME; and toxicity analysis using pkCSM. All data obtained were then analyzed descriptively to assess the relationships among biological activity, physicochemical characteristics, bioavailability, and toxicity levels for each compound.

The initial stage of the study involved collecting data on galangal secondary metabolites from scientific literature, research articles, and chemical databases. The compounds analyzed included monoterpenes, sesquiterpenes, flavonoids, phenolics, and diterpenoids known to occur in galangal. These compounds included eugenol, methyleugenol, beta-pinene, alpha-pinene, alpha-farnesene, alpha-caryophyllene, 4-terpineol, (+)-camphor, galangin, galanganol A, galanganol B, galanganol C, galanal A, galanal B, aframodial, galanolactone, trans-*p*-hydroxycinnamaldehyde, trans-*p*-coumaryl alcohol, 1'-Acetoxychavicol acetate, and 1'-Acetoxyeugenol acetate. The chemical structures of each compound were obtained from the PubChem database in Simplified Molecular Input Line Entry System (SMILES) format. The SMILES format was used because it can be directly processed by various bioinformatics and computational chemistry platforms.

Antifungal activity analysis was conducted using the PASS Online (Prediction of Activity Spectra for Substances) platform. PASS Online is a computational software tool used to predict the possible biological activity of compounds based on structural similarity to previously identified active compounds. The SMILES structures of each compound were entered into the PASS Online system to obtain probability of activity (Pa) and probability of inactivity (Pi) values. The Pa value was used as an indicator of the compounds' potential antifungal activity. Compounds with Pa values greater than Pi and closer to 1 were predicted to have higher potential for biological activity. The prediction results were then used to identify the most promising secondary metabolites of galangal as natural antifungal candidates.

The next stage involved physicochemical properties and pharmacokinetic analysis using the SwissADME platform. SwissADME was used to evaluate molecular characteristics related to absorption capability, distribution, membrane permeability, and compound bioavailability. The physicochemical parameters analyzed included molecular weight, heavy atoms, aromatic heavy atoms, hydrogen-bond donors, hydrogen-bond acceptors, molar refractivity, topological polar surface area (TPSA), and fraction Csp3. Molecular weight was used to determine compound size,

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while TPSA was used to estimate biological membrane penetration and oral absorption potential. Hydrogen-bond donor and acceptor parameters were analyzed to assess compounds' ability to form hydrogen bonds, which influence biological interactions.

In addition to physicochemical properties, SwissADME was also used to analyze water solubility, lipophilicity, and bioavailability score. Water solubility was assessed using Log S values from the ESOL method. Lipophilicity was analyzed using consensus Log P o/w values, which indicate the balance between hydrophilic and lipophilic properties of compounds. Meanwhile, the bioavailability score was used to estimate the probability of oral absorption of compounds based on pharmacokinetic parameters and Lipinski's rule. Compounds with high bioavailability scores were predicted to exhibit greater biological absorption.

Drug-likeness analysis was also performed using SwissADME based on several major rules, namely Lipinski, Veber, Ghose, Egan, and Muegge rules. Lipinski's rule was used to predict oral absorption potential based on molecular weight, lipophilicity, and the counts of hydrogen-bond donors and acceptors. Veber's rule was used to evaluate molecular flexibility and compound polarity. Meanwhile, the Ghose, Egan, and Muegge rules were used to assess the suitability of molecular characteristics for ideal drug candidates. Compounds that met most of these parameters were predicted to exhibit favorable pharmacokinetic properties and biological permeability, making them potential candidates for natural product-based antifungal agents.

Toxicity analysis was performed using the pkCSM platform to predict the biological safety of galangal secondary metabolites. The analyzed toxicity parameters included AMES toxicity, hepatotoxicity, *Tetrahymena pyriformis* toxicity, and Minnow toxicity. AMES toxicity was used to predict the mutagenic potential of compounds by assessing the likelihood of genetic alterations. Hepatotoxicity was used to estimate the potential toxic effects on the liver. *Tetrahymena pyriformis* toxicity was used to evaluate toxicity toward protozoan organisms, while Minnow toxicity was used to estimate toxicity impacts on aquatic organisms such as small fish. The toxicity prediction results were used to evaluate compound safety before the compounds were considered natural antifungal candidates.

All data obtained from PASS Online, SwissADME, and pkCSM analyses were then organized into tables and analyzed descriptively. Data interpretation was performed by comparing the antifungal activity values, physicochemical characteristics, bioavailability, drug-likeness, and toxicity profiles of each compound with those reported in the recent scientific literature. The analysis was conducted to determine the relationships among the chemical structure, physicochemical properties, and biological activity of galangal secondary metabolites as natural product-based antifungal candidates. The results of this study are expected to provide scientific information on the biological potential and safety of galangal secondary metabolites, thereby serving as a basis for developing safer, more effective, and environmentally friendly natural antifungal agents.

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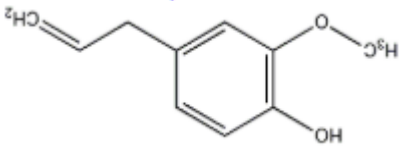
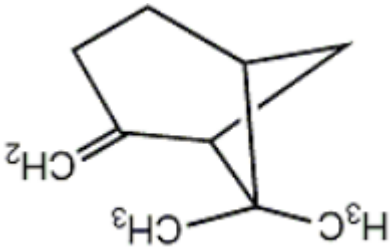
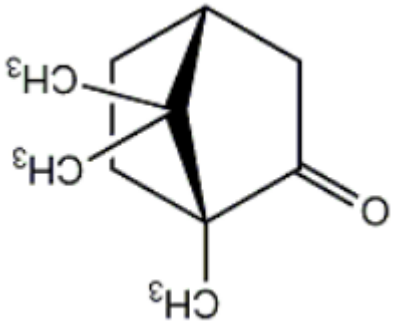
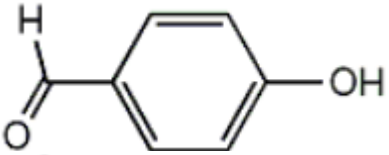
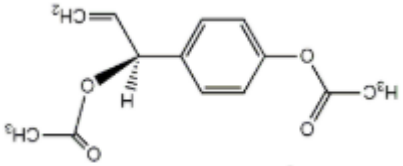
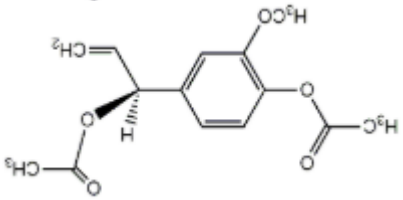
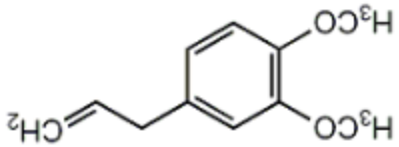
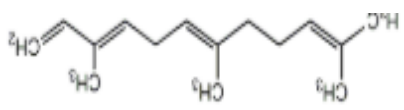
RESULTS AND DISCUSSION

Table 1. Structural Images of Compounds from Alpinia galanga

Nu	Compound Name	Chemical Structure
1	Eugenol	
2	beta-Pinene	
3	(+)-Camphor	
4	4-Hydroxybenzaldehyde	
5	1'-Acetoxychavicol acetate (ACA)	
6	1'-Acetoxyeugenol acetate (AEA)	
7	Methyleugenol	
8	alpha-Farnesene	

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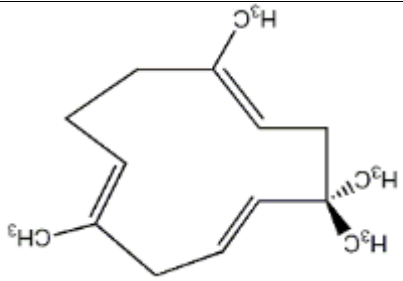
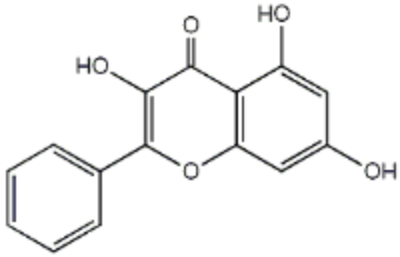
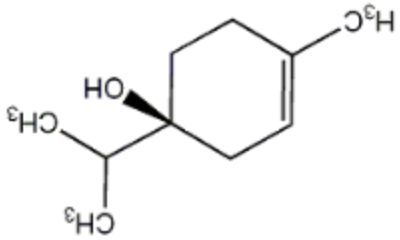
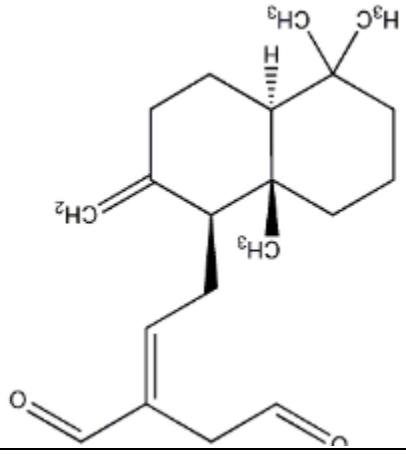
Nu	Compound Name	Chemical Structure
9	alpha-Caryophyllene (obsol.) (α-CAR)	
10	Galangin	
11	Origanol	
12	(E)-Labda-8(17),12-diene-15,16-dial (ELDD)	

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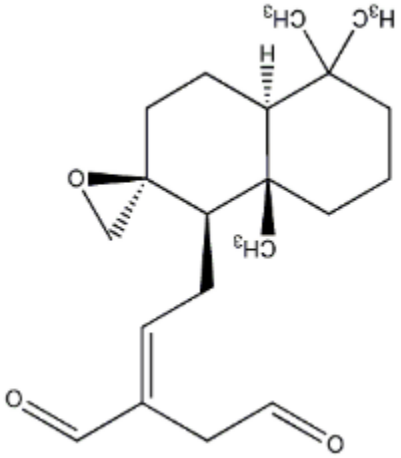
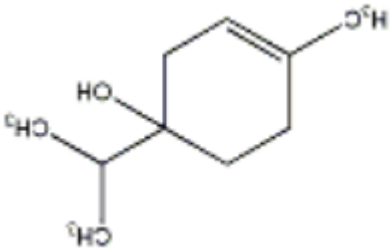
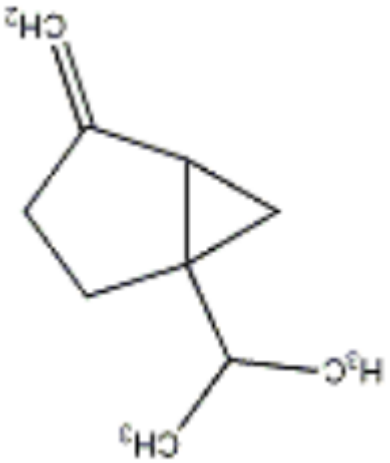
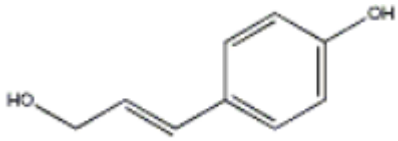
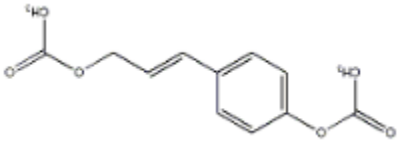
Nu	Compound Name	Chemical Structure
13	Aframodial	
14	4-Terpineol	
15	4(10)-Thujene	
16	trans-p-Coumaryl alcohol	
17	trans-p-Coumaryl diacetate	

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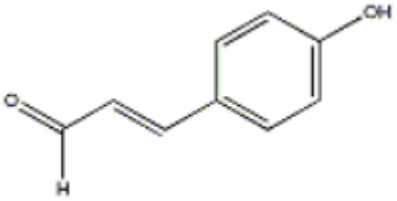
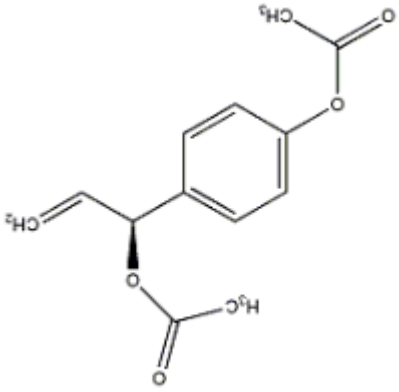
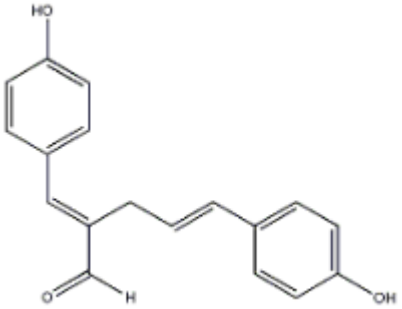
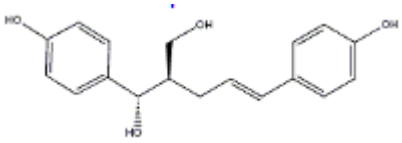
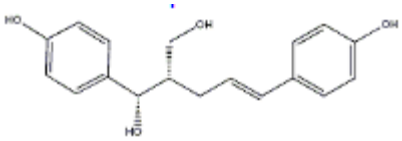
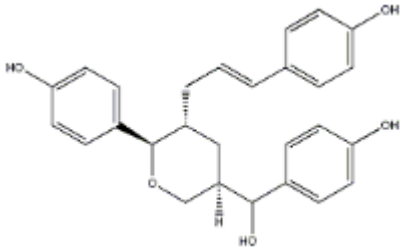
Nu	Compound Name	Chemical Structure
18	trans-p-Hydroxycinnamaldehyde (PHCA)	
19	1'S-1'-Acetoxychavicol acetate (SACA)	
20	Galanganal	
21	Galanganol A	
22	Galanganol B	
23	Galanganol C	

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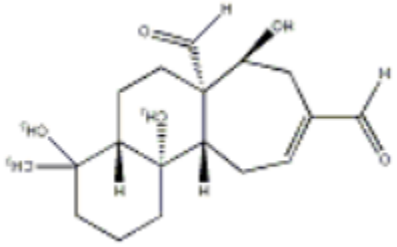
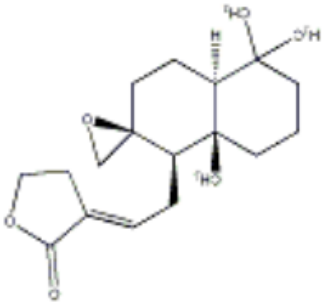
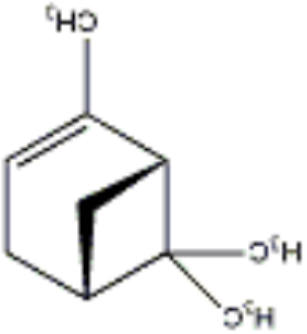
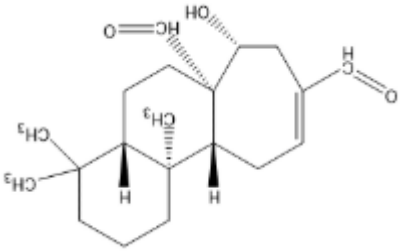
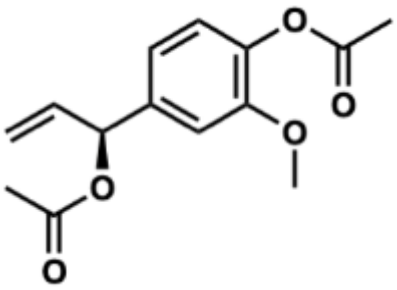
Nu	Compound Name	Chemical Structure
24	Galanal A	
25	Galanolactone	
26	1R,5R-(+)-alpha-Pinene(α-PIN)	
27	Galanal B	
28	1'-Acetoxyeugenol acetate. (AEA.)	

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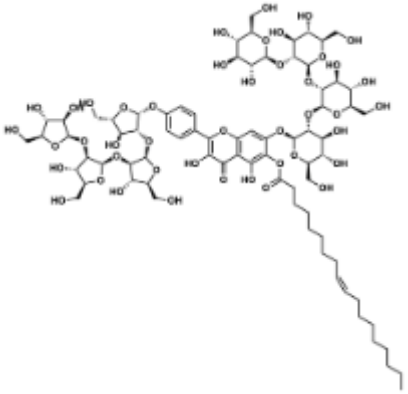
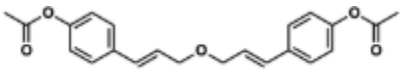
Nu	Compound Name	Chemical Structure
29	AG 11	
30	Bis(4-acetoxycinnamyl) ether (BACE)	
31	1'-Hydroxychavicol acetate (HCA)	

Table 2. SMILES (Simplified Molecular Input Line Entry System) of Compounds in *Alpinia galanga*

Nu	Compound	SMILES Code
1	Eugenol	C=CCc1ccc(O)c(OC)c1
2	beta-Pinene	C=C1CCC2CC1C2(C)C
3	(+)-Camphor	CC1(C)[C@@H]2CC[C@@]1(C)C(=O)C2
4	4-Hydroxybenzaldehyde	O=Cc1ccc(O)cc1
5	ACA	C=C[C@H](OC(C)=O)c1ccc(OC(C)=O)cc1
6	AEA	C=C[C@H](OC(C)=O)c1ccc(OC(C)=O)c(OC)c1
7	Methyleugenol	C=CCc1ccc(OC)c(OC)c1
8	alpha-Farnesene	C=C/C(C)=C/C/C=C(C)CCC=C(C)C
9	α-CAR	C/C1=CCC/C(C)=C/CC(C)(C)/C=C/C1
10	Galangin	O=c1c(O)c(-c2ccccc2)oc2cc(O)cc(O)c12
11	Origanol	CC1=CC[C@](O)(C(C)C)CC1
12	ELDD	C=C1CC[C@H]2C(C)(C)CCC[C@]2(C)[C@H]1C/C=C(/C=O)CC=O
13	Aframodial	CC1(C)CCC[C@@]2(C)[C@H]1CC[C@@]1(CO1)[C@@H]2C/C=C(/C=O)CC=O
14	4-Terpineol	CC1=CCC(O)(C(C)C)CC1
15	4(10)-Thujene	C=C1CCC2(C(C)C)CC12
16	trans-p-Coumaryl alcohol	OC/C=C/c1ccc(O)cc1 OC/C=C/c1ccc(O)cc1
17	trans-p-Coumaryl diacetate	CC(=O)OC/C=C/c1ccc(OC(C)=O)cc1
18	PHCA	O=C/C=C/c1ccc(O)cc1
19	ACA	C=C[C@H](OC(C)=O)c1ccc(OC(C)=O)cc1
20	Galanganal	O=C/C(=C/c1ccc(O)cc1)C/C=C/c1ccc(O)cc1
21	Galanganol A	OC[C@@H](C/C=C/c1ccc(O)cc1)[C@H](O)c1ccc(O)cc1
22	Galanganol B	OC[C@H](C/C=C/c1ccc(O)cc1)[C@H](O)c1ccc(O)cc1
23	Galanganol C	Oc1ccc(/C=C/C[C@@H]2C[C@@H](C(O)c3ccc(O)cc3)CO[C@H]2c2ccc(O)cc2)cc1
24	Galanal A	CC1(C)CCC[C@]2(C)[C@H]3CC=C(C=O)C[C@H](O)[C@]3(C=O)CC[C@@H]12
25	Galanolactone	CC1(C)CCC[C@@]2(C)[C@H]1CC[C@@]1(CO1)[C@@H]2C/C=C1CCOC1=O

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Nu	Compound	SMILES Code
26	α-PIN	CC1=CC[C@@H]2C[C@H]1C2(C)C
27	Galanal B	CC1(C)CCC[C@]2(C)[C@H]3CC=C(C=O)C[C@@H](O)[C@]3(C=O)CC[C@@H]12
28	AEA.	C=C[C@H](OC(C)=O)c1ccc(OC(C)=O)c(OC)c1
29	AG 11	CCCCCCCC/C=CCCCCCCCC(=O)Oc1c(O[C@@H]2O[C@H](CO)[C@@H](O)[C@H](O)[C@H]2O[C@@H]2O[C@H](CO)[C@@H](O)[C@H](O)[C@H]2O[C@@H]2O[C@H](CO)[C@@H](O)[C@H](O)[C@H]2O[C@@H]2O[C@H](CO)[C@@H](O)[C@H](O)[C@H]2O)cc2oc(-c3ccc(O[C@H]4O[C@@H](CO)[C@H](O)[C@H]4O[C@H]4O[C@@H](CO)[C@H](O)[C@H]4O[C@H]4O[C@@H](CO)[C@H](O)[C@H]4O[C@H]4O[C@@H](CO)[C@H](O)[C@H]4O)cc3)c(O)c(=O)c2c1O
30	BACE	CC(=O)Oc1ccc(/C=C/COC/C=C/c2ccc(OC(C)=O)cc2)cc1
31	HCA	-

Table 3. Antifungal data of the *Alpinia Galanga* plant based on analysis using PASS online

Nu	Metabolite	PA % Antifungal
1	Eugenol	0,46
2	beta-Pinene	0,225
3	(+)-Camphor	0,27
4	4-Hydroxybenzaldehyde	0,481
5	ACA	0,447
6	AEA	0,603
7	Methyleugenol	0,414
8	alpha-Farnesene	0,636
9	α-CAR	0,339
10	Galangin	0,493
11	Origanol	0,466
12	ELDD	0,436
13	Aframodial	0,269
14	4-Terpineol	0,466
15	4(10)-Thujene	0,34
16	trans-p-Coumaryl alcohol	0,453
17	trans-p-Coumaryl diacetate	0,453
18	PHCA	0,539
19	ACE	0,447
20	Galanganal	0,449
21	Galanganol A	0,535
22	Galanganol B	0,535
23	Galanganol C	0,369
24	Galanal A	0,577
25	Galanolactone	-
26	α-PIN	0,439
27	Galanal B	0,577
28	AEA.	0,603

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Nu	Metabolite	PA % Antifungal
29	AG 11	-
30	BACE	0,414
31	HCA	-

Table 4a. In Silico Data from SwissADME Supporting the Antifungal Activity of *Alpinia galanga* Against Fungi in Galangal Plants

Nu	Compound	Water Solubility		Lipophilicity (LogP)	Bioavailability score
		Log S (ESOL)	Class	Consensus Log P $_{o/w}$	
1	Eugenol	-1.03	Very soluble	-	0.55
2	beta-Pinene	-0.68	Very soluble	-	0.55
3	(+)-Camphor	-0.78	Very soluble	-	0.55
4	4-Hydroxybenzaldehyde	-1.02	Very soluble	-	0.55
5	ACA	-1.16	Very soluble	-	0.55
6	AEA	-1.25	Very soluble	-	0.55
7	Methyleugenol	-1.02	Very soluble	-	0.55
8	alpha-Farnesene	-0.71	Very soluble	-	0.55
9	α -CAR	-1.11	Very soluble	-	0.55
10	Galangin	-2.04	Soluble	-	0.55
11	Origanol	-2.78	Soluble	-	0.55
12	ELDD	-4.19	Moderately soluble	-	0.55
13	Aframodial	-3.76	Soluble	-	0.55
14	4-Terpineol	-2.78	Soluble	-	0.55
15	4(10)-Thujene	-2.57	Soluble	-	0.55
16	trans-p-Coumaryl alcohol	-1.87	Very soluble	-	0.55
17	trans-p-Coumaryl diacetate	-2.42	Soluble	-	0.55
18	PHCA	-2.13	Soluble	-	0.55
19	ACE	-2.55	Soluble	-	0.55
20	Galanganal	-3.98	Soluble	-	0.55
21	Galanganol A	-3.30	Soluble	-	0.55
22	Galanganol B	-3.30	Soluble	-	0.55
23	Galanganol C	-5.46	Moderately soluble	-	0.55
24	Galanal A	-4.33	Moderately soluble	-	0.55
25	Galanolactone	-4.60	Moderately soluble	-	0.55
26	A-PIN	-3.51	Soluble	-	0.55
27	Galanal B	-4.33	Moderately soluble	-	0.55
28	AEA.	-2.62	Soluble	-	0.55
29	AG 11	-	-	-	-
30	BACE	-4.21	Moderately	-	0.55

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Nu	Compound	Water Solubility		Lipophilicity (LogP)	Bioavailability score
		Log S (ESOL)	Class	Consensus Log P o/w	
31	HCA		soluble		

Table 4b. In Silico Drug-Likeness Data from SwissADME Supporting the Antifungal Activity of *Alpinia galanga* Against Fungi in Galangal Plants

Nu	Compound	Drug-Likeness				
		Lipinski	Ghose	Veber	Egan	Muegge
1	Eugenol	Yes	Yes	Yes	Yes	No
2	beta-Pinene	Yes	No	Yes	Yes	No
3	(+)-Camphor	Yes	No	Yes	Yes	No
4	4-Hydroxybenzaldehyde	Yes	No	Yes	Yes	No
5	ACA	Yes	Yes	Yes	Yes	Yes
6	AEA	Yes	Yes	Yes	Yes	Yes
7	Methyleugenol	Yes	Yes	Yes	Yes	No
8	alpha-Farnesene	Yes	Yes	Yes	Yes	No
9	α -CAR	Yes	Yes	Yes	Yes	No
10	Galangin	Yes	Yes	Yes	Yes	Yes
11	Origanol	Yes	No	Yes	Yes	No
12	ELDD	Yes	Yes	Yes	Yes	Yes
13	Aframodial	Yes	Yes	Yes	Yes	Yes
14	4-Terpineol	Yes	No	Yes	Yes	No
15	4(10)-Thujene	Yes	No	Yes	Yes	No
16	trans-p-Coumaryl alcohol	Yes	No	Yes	Yes	No
17	trans-p-Coumaryl diacetate	Yes	Yes	Yes	Yes	Yes
18	PHCA	Yes	No	Yes	Yes	No
19	1'S-1'-Acetoxychavicol acetate	Yes	Yes	Yes	Yes	Yes
20	Galanganal	Yes	Yes	Yes	Yes	Yes
21	Galanganol A	Yes	Yes	Yes	Yes	Yes
22	Galanganol B	Yes	Yes	Yes	Yes	Yes
23	Galanganol C	Yes	Yes	Yes	Yes	Yes
24	Galanal A	Yes	Yes	Yes	Yes	Yes
25	Galanolactone	Yes	Yes	Yes	Yes	Yes
26	α-PIN	Yes	No	Yes	Yes	No
27	Galanal B	Yes	Yes	Yes	Yes	Yes
28	AEA.	Yes	Yes	Yes	Yes	Yes
29	AG 11	-	-	-	-	-
30	BACE	Yes	Yes	Yes	Yes	Yes
31	HCA	-	-	-	-	-

Table 4c. In Silico Physicochemical Properties Data from SwissADME Supporting the Antifungal Activity of *Alpinia galanga* Against Fungi in Galangal Plants

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Nu	Compound	Physicochemical Properties							
		Mol. Weight (g/mol)	Num heavy atoms	Num. arom heavy atoms	Fraction Csp3	Num. H-bond acceptors	Num. H-bond donors	Molar refractivity	TPSA (Å²)
1	Eugenol	164.20	12	6	0.20	2	1	49.06	29.46
2	beta-Pinene	136.23	10	0	0.80	0	0	45.22	0.00
3	(+)-Camphor	152.23	11	0	0.90	1	0	45.64	17.07
4	4-Hydroxybenzaldehyde	122.12	9	6	0.00	2	1	33.85	37.30
5	ACA	234.25	17	6	0.23	4	0	62.95	52.60
6	AEA	264.27	19	6	0.29	5	0	69.44	61.83
7	Methyleugenol	178.23	13	6	0.27	2	0	53.53	18.46
8	alpha-Farnesene	204.35	15	0	0.47	0	0	72.32	0.00
9	α-CAR	204.35	15	0	0.60	0	0	70.42	0.00
10	Galangin	270.24	20	16	0.00	5	3	73.99	90.90
11	Origanol	154.25	11	0	0.80	1	1	48.80	20.23
12	ELDD	302.45	22	0	0.70	2	0	92.96	34.14
13	Aframodial	318.45	23	0	0.80	3	0	92.44	46.67
14	4-Terpineol	154.25	11	0	0.80	1	1	48.80	20.23
15	4(10)-Thujene	136.23	10	0	0.80	0	0	45.22	00.00
16	trans-p-Coumaryl alcohol	150.17	11	6	0.11	2	2	44.52	40.46
17	trans-p-Coumaryl diacetate	234.25	17	6	0.23	4	0	63.74	52.60
18	PHCA	148.16	11	6	0.00	2	1	43.56	37.30
19	ACE	234.25	17	6	0.23	4	0	62.95	52.60
20	Galanganal	280.32	21	12	0.06	3	2	84.81	57.53
21	Galanganol A	300.35	22	12	0.22	4	4	86.62	80.92
22	Galanganol B	300.35	22	12	0.22	4	4	86.62	80.92
23	Galanganol C	432.51	32	18	0.26	5	4	125.36	90.15
24	Galanal A	318.45	23	0	0.80	3	1	92.22	54.37
25	Galanolactone	318.45	23	0	0.85	3	0	91.21	38.83
26	α-PIN	136.23	10	0	0.80	0	0	45.22	0.00
27	Galanal B	318.45	23	0	0.80	3	1	92.22	54.37
28	AEA.	264.27	19	6	0.29	5	0	69.44	61.83

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Nu	Compound	Physicochemical Properties							
		Mol. Weight (g/mol)	Num heavy atoms	Num. arom heavy atoms	Fraction Csp3	Num. H-bond acceptors	Num. H-bond donors	Molar refractivity	TPSA (Å²)
29	AG 11	-	-	-	-	-	-	-	-
30	BACE	366.41	27	12	0.18	5	0	104.65	61.83
31	HCA	-	-	-	.-	-	-	-	-

Table 5. In Silico Data of *Alpinia galanga from* pkCSM

Nu	Compound	AMES Toxicity	Hepatotoxcity	Environmental Toxicity	
				T.pyriformis toxicity(Log ug/L)	Minnow toxicity(log Mm)
1.	Eugenol	Yes	No	0.764	1.048
2.	beta-Pinene	No	No	0.633	1.131
3.	(+)-Camphor	No	No	0.267	1.34
4.	4-Hydroxybenzaldehyde	No	No	-0.297	1.868
5.	ACA	No	No	0.71	1.801
6.	AEA	No	No	0.485	1.722
7.	Methyleugenol	No	No	1.147	0.938
8.	alpha-Farnesene	No	No	2.09	-0.537
9.	α-CAR	No	No	1.451	0.716
10.	Galangin	Yes	No	0.348	0.45
11.	Origanol	No	No	0.36	1.576
12.	ELDD	No	Yes	0.962	-0.883
13.	Aframodial	No	No	0.824	0.025
14.	4-Terpineol	No	No	0.36	1.576
15.	4(10)-Thujene	No	No	0.85	0.735
16.	trans-p-Coumaryl alcohol	-	-	-	-
17.	trans-p-Coumaryl diacetate	No	No	0.914	0.686
18.	PHCA	No	No	0.7	1.445
19.	ACE	No	No	0.71	1.801
20.	Galanganal	No	No	0.532	0.38
21	Galanganol A	Yes	No	0.611	0.966
22	Galanganol B	Yes	No	0.611	0.966
23	Galanganol C	No	No	0.296	-0.88
24	Galanal A	No	No	0.648	0.082
25	Galanolactone	No	No	1.009	0,084
26	α-PIN	No	No	0.45	1.159
27	Galanal B	No	No	0,648	0,082
28	AEA	No	No	0,485	1.722
29	AG 11	No	No	0,285	27.884
30	BACE	No	No	0,57	-1.209
31	HCA	-	-	-	-

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Based on the analysis results from PASS Online, secondary metabolites in galangal (*Alpinia galanga*) demonstrated considerable potential for antifungal activity. The probability of activity (Pa) quantifies the likelihood that a compound exhibits a particular biological activity, with values closer to 1 indicating a higher probability of biological activity. The results presented in the table show that most compounds had Pa values above 0.5, suggesting their potential as natural antifungal agents. The compound with the highest value was alpha-farnesene (0.636), followed by 1'-Acetoxyeugenol acetate (0.603), galanal A and galanal B (0.577), as well as galanganol A and galanganol B with values ranging from 0.535 to 0.539. These high probability values indicate that secondary metabolites in galangal belonging to the terpenoid, flavonoid, and phenolic groups exhibit significant biological activity against pathogenic fungi. Meanwhile, several compounds such as eugenol, origanol, 4-terpineol, and trans-*p*-coumaryl alcohol exhibited moderate Pa values ranging from 0.45–0.46, which still indicate potential biological activity. These findings suggest that galangal contains a broad spectrum of bioactive metabolites with promising potential for development as a natural antifungal source (Merino-Ramirez & Salvador-Reyes, 2026).

Terpenoid compounds such as alpha-farnesene, beta-pinene, alpha-caryophyllene, alpha-pinene, and 4(10)-thujene are known to exert antifungal mechanisms through disruption of fungal cell membrane integrity. Alpha-farnesene, which showed the highest Pa value, is predicted to play an important role in galangal's antifungal activity because its hydrophobic nature enables direct interaction with the lipid bilayer of microbial membranes. Membrane damage results in leakage of ions and intracellular components, thereby disrupting fungal cell metabolism. In addition, sesquiterpene compounds such as alpha-caryophyllene are also known to inhibit mycelial growth and biofilm formation in pathogenic fungi. Recent studies have shown that galangal essential oil, which is rich in terpenoid compounds, exhibits strong inhibitory activity against various plant- and human-pathogenic fungi. Although compounds such as beta-pinene and alpha-caryophyllene showed lower Pa values than alpha-farnesene, the combination of these volatile compounds may still provide synergistic effects that contribute to the overall antifungal activity of galangal extract (Ciobotaru *et al*., 2025).

Flavonoid and phenolic compounds such as galangin, galanganol A–C, trans-*p*-hydroxycinnamaldehyde, and eugenol also demonstrated considerable antifungal activity. Galangin exhibited a Pa value of 0.493, while galanganol A and galanganol B showed higher values of approximately 0.535. Flavonoids are known to act by inhibiting cell wall synthesis, disrupting energy metabolism, and increasing oxidative stress in fungal cells. The presence of hydroxyl groups in flavonoid structures enhances their ability to form hydrogen bonds with microbial target proteins and enzymes, thereby strengthening their biological activity. Eugenol, one of the major components of galangal essential oil, is also recognized for its strong antimicrobial activity through mechanisms involving plasma membrane disruption and increased cell permeability. Recent studies have demonstrated that flavonoids and phenolic compounds derived from herbal plants possess synergistic abilities in inhibiting pathogenic fungal growth, making them promising candidates as safer natural antifungal alternatives compared to synthetic fungicides (Aboody & Mickymaray, 2020).

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Acetoxychavicol derivatives and diterpenoid compounds such as 1'-Acetoxyeugenol acetate, aframodial, galanal A, galanal B, and galanolactone showed relatively high biological activity based on PASS Online predictions. The compound 1'-Acetoxyeugenol acetate exhibited a Pa value of 0.603, suggesting it may be among the most promising antifungal candidates in galangal. Acetoxychavicol derivatives are known to possess antimicrobial, anti-inflammatory, and antioxidant activities by modulating microbial metabolism and inhibiting free radical formation. Furthermore, diterpenoid compounds such as galanal A and galanal B possess lipophilic properties that support interaction with fungal cell membranes, leading to permeability disruption and cell death. Several recent studies have reported that acetoxychavicol acetate compounds from galangal exhibit broad biological activity against pathogenic microorganisms and have strong potential for development as active ingredients in plant-based natural antifungal agents (Janssen & Scheffer, 1985).

Based on the SwissADME analysis results, most active compounds in galangal exhibited pharmacokinetic profiles consistent with their biological activity as antifungal agents. Parameters such as water solubility, lipophilicity, and bioavailability score indicated that the majority of compounds possess a favorable balance between hydrophilic and lipophilic properties. The Log S values for most compounds were categorized as soluble to very soluble, indicating their diffusion capacity and biological distribution. Compounds such as eugenol, beta-pinene, (+)-camphor, and 4-hydroxybenzaldehyde demonstrated high solubility with Log S values ranging from −0.68 to −1.03. Good solubility enables compounds to interact more easily with microbial cell membranes, thereby enhancing antifungal effectiveness. Recent studies have reported that compounds with favorable solubility tend to exhibit more effective bioactivity because they can reach biological targets more efficiently (Tarahi *et al*., 2026).

Flavonoid and diterpenoid compounds such as galangin, galanganol, aframodial, galanal A, galanal B, and galanolactone exhibited lower Log S values and were therefore classified as soluble to moderately soluble. Although these compounds have lower water solubility, their hydrophobic properties facilitate penetration of fungal lipid membranes. The balance between hydrophilic and lipophilic characteristics is an important factor in antifungal activity because compounds must be able to diffuse within biological environments while also penetrating microbial cell membranes. In addition, nearly all compounds had a bioavailability score of 0.55, indicating a relatively high likelihood of oral absorption. These findings suggest that the secondary metabolites of galangal possess pharmacokinetic characteristics that support their development as herbal medicine candidates or natural biofungicides. Recent studies have explained that flavonoid and terpenoid compounds with high bioavailability exhibit greater effectiveness in inhibiting the growth and biofilm formation of pathogenic fungi (Tuan & Masak, 2026).

Drug-likeness analysis using SwissADME demonstrated that most secondary metabolites of galangal complied with Lipinski, Veber, Egan, Ghose, and Muegge rules. Compliance with these parameters indicates that the compounds possess appropriate molecular size, flexibility, polarity, and lipophilic properties to support oral absorption and biological permeability. Compounds such as 1'-Acetoxychavicol acetate, 1'-Acetoxyeugenol acetate, galangin, aframodial,

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galanganol A–C, galanal A–B, and galanolactone showed the best results because they fulfilled nearly all drug-likeness parameters. These characteristics indicate that galangal secondary metabolites exhibit good molecular stability and membrane-penetrating capability, making them highly promising as natural antifungal candidates. Recent studies have emphasized that the drug-likeness approach is highly important in the early screening of natural compounds, as it can accelerate the identification of safe and effective drug candidates before further biological testing (Thomford *et al*., 2018).

Several volatile compounds, such as beta-pinene, (+)-camphor, origanol, and 4-terpineol, showed deviations from the Ghose or Muegge parameters due to their relatively small molecular size and specific lipophilic properties. Nevertheless, these compounds still complied with Lipinski and Veber rules, indicating that they retain strong potential biological activity. Volatile terpenoid compounds are known to penetrate microbial cell membranes effectively due to their high hydrophobicity. Eugenol and methyleugenol also demonstrated favorable drug-likeness profiles and are known to exhibit antifungal activity through mechanisms involving cell membrane disruption and interference with microbial metabolism. Overall, the drug-likeness results indicate that most secondary metabolites of galangal possess molecular characteristics supportive of their development as natural product-based antifungal candidates (Calegari-Alves *et al*., 2025).

The physicochemical properties analysis showed that most active compounds in galangal possess physicochemical characteristics that support biological activity. Parameters such as molecular weight, topological polar surface area (TPSA), hydrogen-bond donor and acceptor counts, and the fraction Csp3 strongly influence compounds' ability to penetrate biological membranes and interact with microbial targets. Most compounds exhibited molecular weights below 500 and TPSA values below 140, thereby meeting the general characteristics of good oral drug candidates. Monoterpene compounds such as beta-pinene, alpha-pinene, (+)-camphor, and 4-terpineol possessed extremely low TPSA values, even reaching 0, indicating highly hydrophobic properties and facilitating penetration through fungal lipid membranes. In contrast, flavonoid compounds such as galangin and galanganol exhibited higher TPSA values due to the presence of hydroxyl groups that increase polarity and the ability to form hydrogen bonds with biological targets (Sharafan *et al*., 2025).

The acetoxychavicol and diterpenoid compound groups, such as 1'-Acetoxychavicol acetate, 1'-Acetoxyeugenol acetate, aframodial, galanal A, and galanal B, demonstrated relatively ideal physicochemical parameters, with moderate molecular weights and TPSA values ranging from 50 to 90. These values indicate a balance between polar and nonpolar properties, thereby supporting favorable biological permeability. In addition, the high Csp3 values observed in diterpenoid compounds indicate flexible molecular structures that facilitate interactions with microbial lipid membranes. Recent studies have stated that the balance between polarity and lipophilicity is a major factor in determining the effectiveness of natural antimicrobial compounds because it influences molecular stability and interaction capability with biological targets (Sadgrove & Jones, 2019).

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The toxicity prediction results using pkCSM indicated that most galangal secondary metabolites have relatively good biological safety profiles. The majority of compounds showed negative results for both hepatotoxicity and AMES toxicity, suggesting that they are likely non-hepatotoxic and non-mutagenic. These findings are highly important because biological safety is a primary factor in the development of drug candidates and natural product-based biofungicides. Terpenoid compounds such as beta-pinene, alpha-pinene, alpha-farnesene, alpha-caryophyllene, and 4-terpineol exhibited low toxicity levels and are therefore predicted to be relatively safe for humans. Recent studies have reported that natural monoterpenes generally have a favorable safety profile because they are readily metabolized and excreted by the body (Rinaldi Alvarenga *et al*., 2021).

Nevertheless, several compounds, such as eugenol, galangin, galanganol A, and galanganol B, showed positive AMES toxicity results, indicating potential mild mutagenic effects under certain conditions. Flavonoid and phenolic compounds with active hydroxyl groups are known to exhibit pro-oxidant activity at high doses, potentially triggering cellular DNA damage. However, these effects are strongly influenced by concentration, biological conditions, and interactions with other metabolites. In addition, the compound (E)-Labda-8(17),12-diene-15,16-dial demonstrated predicted hepatotoxicity and therefore requires further evaluation through *in vitro* and *in vivo* studies before further development. Regarding environmental toxicity parameters, most compounds exhibited low to moderate toxicity, suggesting they are safer than synthetic fungicides. Overall, the pkCSM results indicate that the majority of secondary metabolites in galangal possess relatively favorable toxicity profiles and support the development of galangal as an environmentally friendly and sustainable source of natural antifungal agents (Chouni & Paul, 2018).

CONCLUSION

Based on *in silico* analyses using PASS Online, SwissADME, and pkCSM, the secondary metabolites of *Alpinia galanga* demonstrated promising antifungal potential, supported by favorable pharmacokinetic, drug-likeness, and physicochemical properties, and relatively low toxicity. These findings indicate that galangal has strong potential to be developed as a source of natural antifungal agents and environmentally friendly biofungicides.

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