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PREDICTION OF ANTIFUNGAL ACTIVITY, DRUG-LIKENESS, AND TOXICITY OF *Curcuma xanthorrhiza* COMPOUNDS USING PASS Online, SwissADME, and PKCSM

PREDIKSI AKTIVITAS ANTIJAMUR, SIFAT SEPERTI OBAT (*Drug-Likeness*), DAN TOKSISITAS SENYAWA *Curcuma xanthorrhiza* MENGGUNAKAN PASS Online, SwissADME, DAN pKCSM

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Abstract

This study aimed to analyze the antifungal potential of bioactive compounds in Java turmeric (*Curcuma xanthorrhiza*) against pathogenic fungi in oil palm plants using an *in silico* approach through PASS Online, SwissADME, and PKCSM. PASS Online analysis showed that the oxygenated sesquiterpene group exhibited the highest antifungal activity compared to monoterpenes and basic curcuminoids. Compounds such as Bisacurone, Bisacurone A, Bisacurone B, and Bisacurone C demonstrated the highest probability activity value of 0.767, while Bisacurone epoxide showed a value of 0.729. These compounds are predicted to act through mechanisms involving plasma membrane disruption, inhibition of ergosterol biosynthesis, and increased oxidative stress in fungal cells. SwissADME analysis indicated that most compounds exhibited physicochemical properties conducive to biological activity, including good solubility, balanced lipophilicity, stable bioavailability scores, and compliance with the Lipinski, Veber, Egan, and Muegge drug-likeness parameters. The bisacurone and epoxide sesquiterpene groups demonstrated the most optimal combination of membrane permeability, structural flexibility, and biological interaction capability. Physicochemical property analysis also revealed that compounds with moderate molecular weight, balanced TPSA values, and optimal numbers of hydrogen-bond donors and acceptors exhibited greater antifungal potential. Meanwhile, PKCSM analysis showed that the majority of compounds were neither mutagenic nor hepatotoxic. Monoterpene compounds and the bisacurone group demonstrated relatively safe environmental toxicity profiles, indicating their potential for development as environmentally friendly biofungicides. However, Bisacurone epoxide showed potential AMES toxicity, indicating the need for further *in vitro* and *in vivo* testing. Overall, the study results indicate that *Curcuma xanthorrhiza* has significant potential as a source of natural antifungal compounds for sustainable control of fungal diseases in oil palm plants with improved environmental safety.

Keywords: *Curcuma xanthorrhiza, antifungal, SwissADME, PKCSM, biofungicide*

Abstrak

Penelitian ini bertujuan untuk menganalisis potensi antijamur dari senyawa bioaktif dalam temulawak (*Curcuma xanthorrhiza*) terhadap jamur patogen pada tanaman kelapa sawit menggunakan pendekatan *in silico* melalui PASS Online, SwissADME, dan pKCSM. Analisis PASS Online menunjukkan bahwa kelompok seskuiterpen teroksigenasi memiliki aktivitas antijamur tertinggi dibandingkan dengan monoterpen dan kurkumonoid dasar. Senyawa seperti *Bisacurone*, *Bisacurone A*, *Bisacurone B*, dan

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Bisacurone C menunjukkan nilai probabilitas aktivitas (*Pa*) tertinggi sebesar 0,767, sedangkan *Bisacurone epoxide* menunjukkan nilai sebesar 0,729. Senyawa-senyawa ini diprediksi bekerja melalui mekanisme yang melibatkan gangguan membran plasma, penghambatan biosintesis ergosterol, serta peningkatan stres oksidatif pada sel jamur. Analisis SwissADME menunjukkan bahwa sebagian besar senyawa memiliki sifat fisikokimia yang mendukung aktivitas biologis, termasuk kelarutan yang baik, lipofisilitas yang seimbang, skor bioavailabilitas yang stabil, serta kepatuhan terhadap parameter *drug-likeness* (kemiripan sifat obat) Lipinski, Veber, Egan, dan Muegge. Kelompok seskuiterpen *bisacurone* dan *epoxide* menunjukkan kombinasi yang paling optimal antara permeabilitas membran, fleksibilitas struktural, dan kemampuan interaksi biologis. Analisis sifat fisikokimia juga mengungkapkan bahwa senyawa dengan berat molekul sedang, nilai TPSA yang seimbang, serta jumlah donor dan akseptor ikatan hidrogen yang optimal menunjukkan potensi antijamur yang lebih baik. Sementara itu, analisis pKCSM menunjukkan bahwa mayoritas senyawa tidak bersifat mutagenik maupun hepatotoksik. Senyawa monoterpen dan kelompok *bisacurone* menunjukkan profil toksisitas lingkungan yang relatif aman, sehingga menandakan potensinya untuk dikembangkan sebagai biofungisida yang ramah lingkungan. Namun, *Bisacurone epoxide* menunjukkan potensi toksisitas AMES, yang mengindikasikan perlunya pengujian *in vitro* dan *in vivo* lebih lanjut. Secara keseluruhan, hasil penelitian menunjukkan bahwa *Curcuma xanthorrhiza* memiliki potensi signifikan sebagai sumber senyawa antijamur alami untuk pengendalian berkelanjutan penyakit jamur pada tanaman kelapa sawit dengan keamanan lingkungan yang lebih baik.

Kata Kunci: *Curcuma xanthorrhiza*, antijamur, SwissADME, pKCSM, biofungisida

INTRODUCTION

Oil palm is one of the main plantation commodities that contributes significantly to the Indonesian economy. The productivity of oil palm is highly influenced by plant health conditions, including diseases caused by pathogenic fungi. Various fungal diseases, such as basal stem rot, leaf spot, and root rot, are major factors contributing to the decline in oil palm production in many tropical regions. Although synthetic fungicides remain the primary method for disease control, their long-term use may cause negative impacts, including pathogen resistance, environmental pollution, and harmful residues affecting non-target organisms (Adkar *et al*., 2025). Therefore, the development of natural-based biofungicides has become an increasingly important alternative in recent years.

One herbal plant with strong potential for development as a natural biofungicide is Curcuma xanthorrhiza, or Java turmeric. This plant is widely recognized as a traditional Indonesian medicinal herb rich in secondary metabolites, including curcuminoids, monoterpenes, and sesquiterpenes. Various studies have shown that the secondary metabolites of Java turmeric possess broad biological activities, including antibacterial, antioxidant, anti-inflammatory, and antifungal properties (Rahmat *et al.*, 2021). Major compounds such as xanthorrhizol, curcumin, beta-caryophyllene epoxide, and bisacurone are known to inhibit the growth of various pathogenic microorganisms through mechanisms including disruption of cell membranes, inhibition of ergosterol biosynthesis, and induction of oxidative stress in fungal cells.

The advancement of bioinformatics technology and *in silico* approaches provides significant opportunities for the rapid and efficient identification of bioactive compounds. *In silico* methods enable researchers to predict biological activities, pharmacokinetic properties, physicochemical characteristics, and toxicity levels of compounds without directly performing all

laboratory testing stages. This approach is considered more cost-effective and time-efficient than conventional methods, especially during the early exploration stage for bioactive compound candidates (Hndeya *et al*., 2026). In modern research, the combination of PASS Online, SwissADME, and PKCSM analyses is widely used to evaluate the potential of natural compounds as drug and biofungicide candidates.

PASS Online is a structure-based biological activity prediction platform that estimates the probability that a compound exhibits specific biological activities using probability activity (Pa) values. The higher the Pa value, the greater the likelihood that the compound possesses the desired biological activity. This approach is highly important in the initial screening process of secondary metabolites because it helps identify potential compounds rapidly (Assouguem *et al*., 2025). In turmeric, several oxygenated sesquiterpene compounds have been reported to exhibit high antifungal probability values, indicating their potential for further development as plant-pathogenic fungal control agents.

In addition to biological activity prediction, the physicochemical characteristics of compounds are also important factors in determining their effectiveness as natural antifungal agents. The SwissADME platform is used to evaluate parameters such as water solubility, lipophilicity (Log P), bioavailability score, drug-likeness, and physicochemical properties. These parameters influence the ability of compounds to penetrate fungal cell membranes, maintain stability in biological systems, and distribute effectively within plant tissues (Parveen *et al*., 2025). Compounds with a balance between solubility and lipophilicity generally exhibit better membrane-penetrating ability, leading to higher biological activity.

The terpenoid compounds found in Java turmeric are known to possess characteristics that support antifungal activity. Monoterpenes such as limonene, alpha-pinene, and beta-myrcene are lipophilic, enabling them to interact with the lipid layers of fungal cell membranes and alter membrane permeability. Meanwhile, oxygenated sesquiterpenes such as beta-caryophyllene epoxide and bisacurone epoxide exhibit higher activity due to the presence of active oxygen groups that enhance interactions with target proteins and enzymes in fungi (de Lacerda Leite *et al*., 2021). Phenolic compounds such as xanthorrhizol and curcumin also contribute to antifungal activity through mechanisms involving inhibition of ergosterol synthesis and induction of reactive oxygen species (ROS) formation.

In the development of natural biofungicides, drug-likeness is also an important parameter used to assess the suitability of compounds' physicochemical properties within biological systems. Drug-likeness evaluation is conducted using several rules, such as Lipinski, Ghose, Veber, Egan, and Muegge. Compounds that fulfill these parameters are predicted to have better absorption, distribution, and biological stability (Sampat *et al*., 2022). Several secondary metabolites of Java turmeric, including curcumin, bisacurone, and curzerenone, have been reported to satisfy most drug-likeness parameters, indicating their strong potential for development as natural bio-based antifungal agents.

Besides biological effectiveness, compound safety is also a crucial aspect in biofungicide development. Toxicity analysis using PKCSM allows the prediction of mutagenic potential, hepatotoxicity, and environmental toxicity of compounds. Bioactive compounds with strong

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antifungal activity but high toxicity are unsuitable for broad application in sustainable agricultural systems. Therefore, toxicity evaluation is necessary to ensure that candidate compounds do not negatively affect non-target organisms or the surrounding environment (Dantas *et al*., 2025). Several studies have shown that most secondary metabolites of Java turmeric possess relatively safe toxicity profiles, supporting their development as environmentally friendly biofungicides.

The use of plant-based herbal biofungicides has strong potential to support sustainable agricultural systems. The use of natural compounds from Java turmeric is expected to reduce dependence on synthetic fungicides while minimizing the risk of pathogen resistance. In addition, the diverse secondary metabolites present in Java turmeric may produce synergistic effects among compounds, resulting in more effective antifungal activity. The combination of monoterpenes, oxygenated sesquiterpenes, and phenolic compounds provides complex mechanisms of action against pathogenic fungi, ranging from cell membrane damage to disruption of intracellular metabolism (Monteiro *et al*., 2026).

Based on the description above, conducting in silico research on the antifungal potential of secondary metabolites from Curcuma xanthorrhiza is important. Analyses using PASS Online, SwissADME, and PKCSM can provide a comprehensive overview of the biological activities, physicochemical characteristics, drug-likeness, and toxicity profiles of the bioactive compounds in Java turmeric. The results of this study are expected to provide a scientific basis for the development of effective, safe, and environmentally friendly natural biofungicides to control pathogenic fungi in oil palm plants.

RESEARCH METHODS

Research Type and Approach

This study employed a descriptive, exploratory approach using an in silico method to analyze the antifungal potential of bioactive compounds from Java turmeric (*Curcuma xanthorrhiza*) against pathogenic fungi in oil palm plants. The *in silico* approach was selected because it is capable of predicting biological activity, pharmacokinetic properties, drug-likeness, physicochemical properties, and compound toxicity rapidly and efficiently before further laboratory testing is conducted (R *et al*., 2025). Computational methods are currently widely used in the development of natural biofungicides because they can accelerate the identification process of active compound candidates with relatively high accuracy (Vasile *et al*., 2025).

Time and Place of Research

The study was conducted online using several bioinformatics platforms and international chemical databases. Data collection and analysis were carried out during January–March 2026. The entire research process was conducted using computer devices with internet access to operate *in silico* analysis software and websites (Roney & Mohd Aluwi, 2024).

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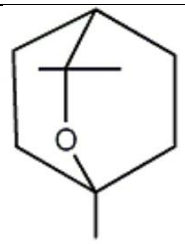
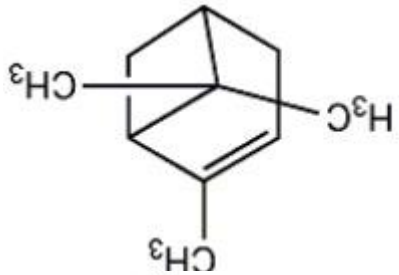
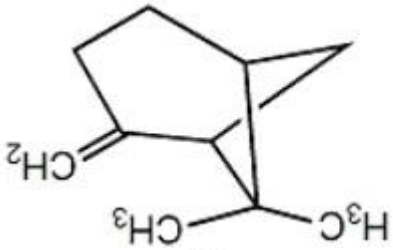
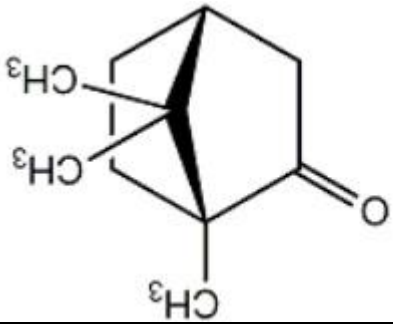
Tools and Materials

The tools used in this study included a laptop, spreadsheet software, and internet access. The research materials consisted of structural data of secondary metabolite compounds from Java turmeric obtained from public chemical compound databases. The analyzed compounds included bisacurone, bisacurone epoxide, xanthorrhizol, curcumin, demethoxycurcumin, limonene, beta-myrcene, beta-caryophyllene epoxide, humulene epoxide, and several other terpenoid compounds known to be present in Java turmeric (Ayati *et al*., 2019).

RESULTS AND DISCUSSION

Table 1. Chemical structures of *Curcuma xanthorrhiza* (Temulawak) compounds

Nu	Compound	Chemical Structure
1	1,8-Cineol	
2	alpha-Pinene	
3	beta-Pinene	
4	(+)-Camphor	

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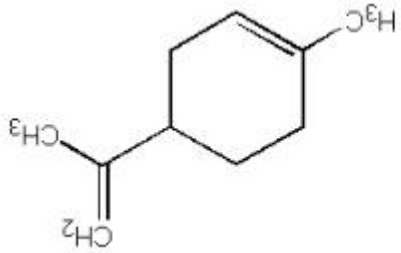
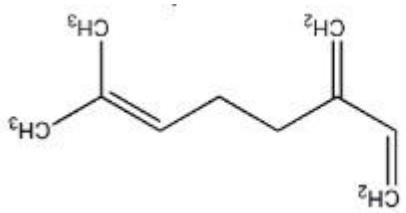
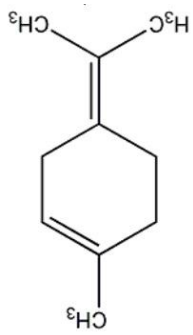
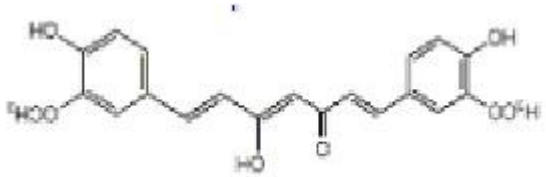
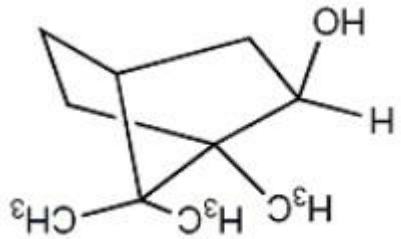
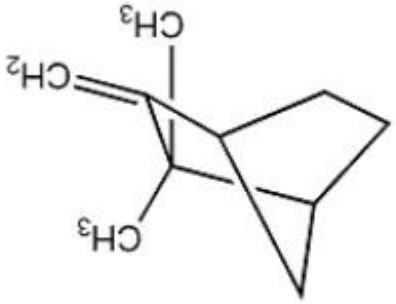
5	Limonene	
6	beta-Myrcene	
7	alpha-Terpinolene	
8	Curcumin	
9	Borneol	
10	Camphene	

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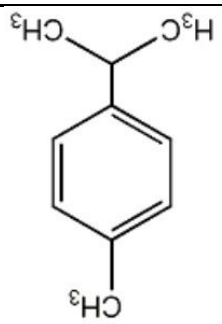
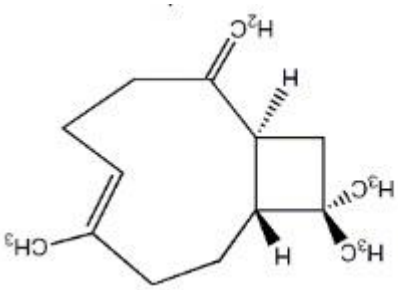
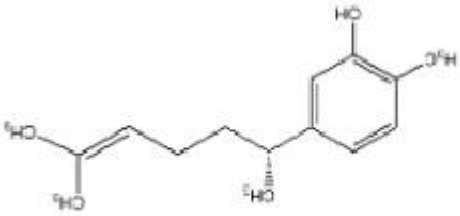
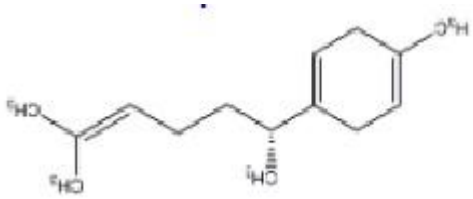
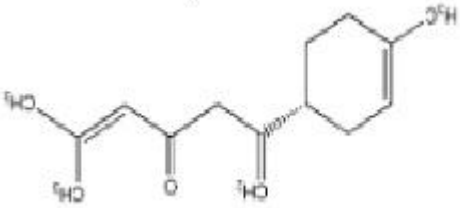
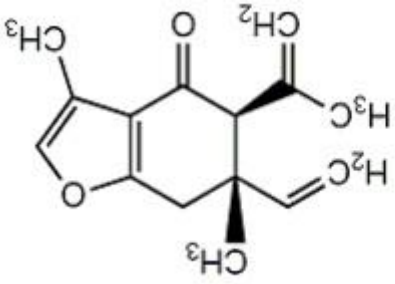
11	p-Cymene	
12	beta-Caryophyllene	
13	(R)-(-)-Xanthorrhizol	
14	beta-Curcumene	
15	(+)-beta-Atlantone	
16	Germacrone	

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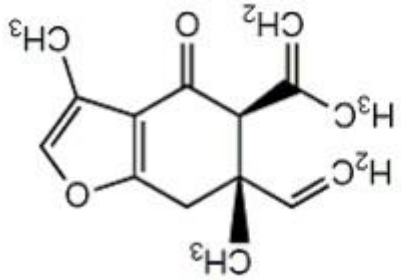
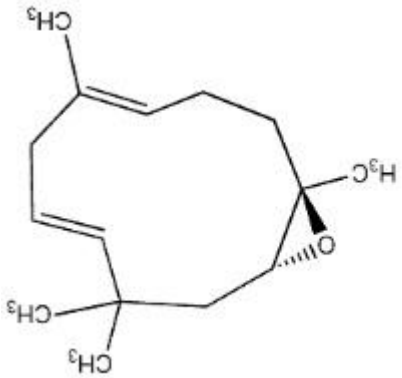
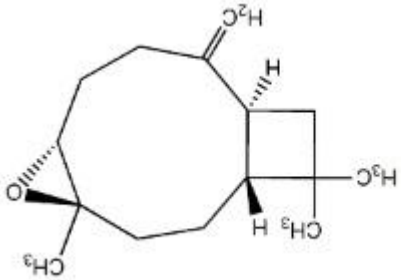
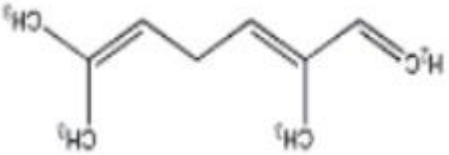
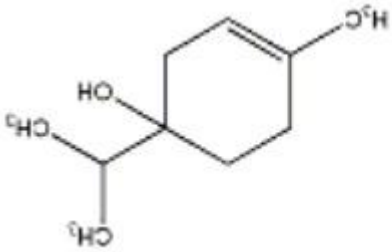
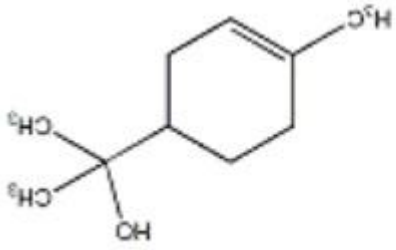
17	Curzerenone	
18	Humulene epoxide	
19	(-)-beta-Caryophyllene epoxide	
20	(E)-beta-Ocimene	
21	4-Terpineol	
22	alpha-Terpineol	

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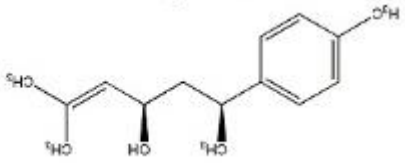
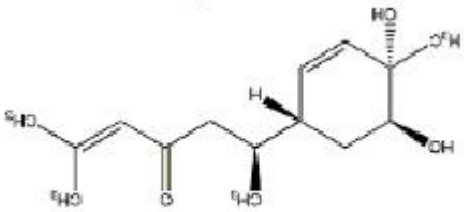
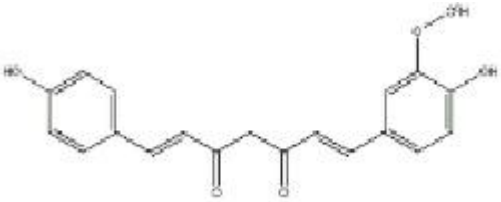
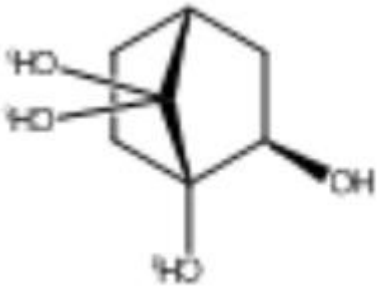
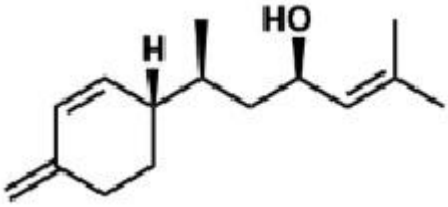
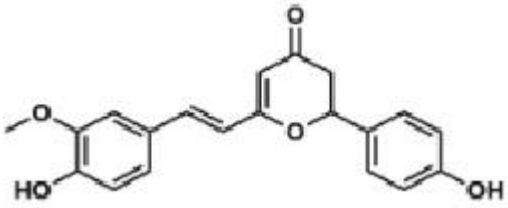
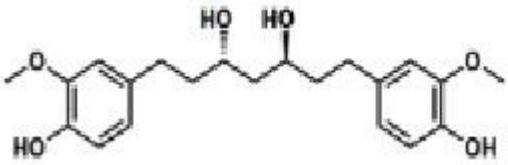
23	Bisacumol	
24	Bisacurone	
25	Demethoxycurcumin	
26	Isoborneol	
27	1,3(15),10-Bisabolatrien-9-ol	
28	3'-Demethoxycyclocurcumin	
29	1,7-Bis(4-hydroxy-3-methoxyphenyl)-3,5-heptanediol (BHMH)	

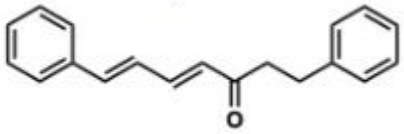
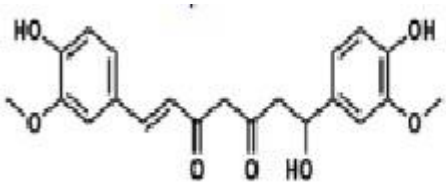
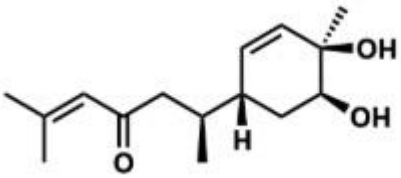
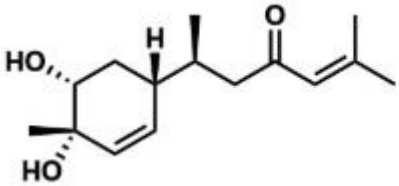
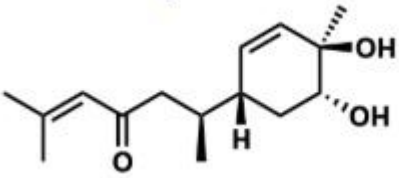
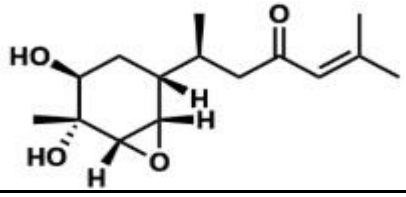
30	Alnustone	
31	1,5-Dihydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-4,6-heptadien-3-one (DHBMH)	
32	Bisacurone A	
33	Bisacurone B	
34	Bisacurone C	
35	Bisacurone epoxide	

Table 2. SMILES code data for *Curcuma xanthorrhiza*

Nu	Compound	SMILES Code
1	1,8-Cineol	CC12CCC(CC1)C(C)(C)O2
2	alpha-Pinene	CC1=CCC2CC1C2(C)C
3	beta-Pinene	C=C1CCC2CC1C2(C)C
4	(+)-Camphor	CC1(C)[C@@H]2CC[C@@]1(C)C(=O)C2
5	Limonene	C=C(C)C1CC=C(C)CC1
6	beta-Myrcene	C=CC(=C)CCC=C(C)C
7	alpha-Terpinolene	CC1=CCC(=C(C)C)CC1
8	Curcumin	COc1cc(/C=C/C(=O)/C=C(O)/C=C/c2ccc(O)c(OC)c2)ccc1O
9	Borneol	CC1(C)C2CCC1(C)C(O)C2
10	Camphene	C=C1C2CCC(C2)C1(C)C
11	p-Cymene	Cc1ccc(C(C)C)cc1

Nu	Compound	SMILES Code
12	beta-Caryophyllene	C=C1CC/C=C(C)CC[C@@H]2[C@@H]1CC2(C)C
13	(R)-(-)-Xanthorrhizol	CC(C)=CCC[C@@H](C)c1ccc(C)c(O)c1
14	beta-Curcumene	CC(C)=CCC[C@@H](C)C1=CCC(C)=CC1
15	(+)-beta-Atlantone	C=C(CC(=O)C=C(C)C)[C@H]1CC=C(C)CC1
16	Germacrone	CC(C)=C1C/C=C(C)CC/C=C(C)CC1=O
17	Curzerenone	C=C[C@]1(C)Cc2occ(C)c2C(=O)[C@H]1C(=C)C
18	Humulene epoxide	C/C1=CCC[C@@]2(C)O[C@@H]2CC(C)(C)/C=C/C1
19	(-)-beta-Caryophyllene epoxide	C=C1CC[C@H]2O[C@]2(C)CC[C@@H]2[C@@H]1CC2(C)C
20	(E)-beta-Ocimene	C=C/C(C)=C/CC=C(C)C
21	4-Terpineol	CC1=CCC(O)(C(C)C)CC1
22	alpha-Terpineol	CC1=CCC(C(C)(C)O)CC1
23	Bisacumol	CC(C)=C[C@H](O)C[C@H](C)c1ccc(C)cc1
24	Bisacurone	CC(C)=CC(=O)C[C@H](C)[C@@H]1C=C[C@](C)(O)[C@@H](O)C1
25	Demethoxycurcumin	COc1cc(/C=C/C(=O)CC(=O)/C=C/c2ccc(O)cc2)ccc1O
26	Isoborneol	CC1(C)[C@@H]2CC[C@@]1(C)[C@H](O)C2
27	1,3(15),10-Bisabolatrien-9-ol	C=C1C=C[C@H]([C@@H](C)C[C@@H](O)C=C(C)C)CC1
28	3'-Demethoxycyclocurcumin	COc1cc(/C=C/C2=CC(=O)CC(c3ccc(O)cc3)O2)ccc1O
29	BHMH	COc1cc(CC[C@H](O)C[C@@H](O)CCc2ccc(O)c(OC)c2)ccc1O
30	Alnustone	O=C(/C=C/C=C/c1ccccc1)CCc1ccccc1
31	DHBMH	COc1cc(/C=C/C(=O)CC(=O)CC(O)c2ccc(O)c(OC)c2)ccc1O
32	Bisacurone A	CC(C)=CC(=O)C[C@H](C)[C@@H]1C=C[C@@](C)(O)[C@@H](O)C1
33	Bisacurone B	CC(C)=CC(=O)C[C@H](C)[C@@H]1C=C[C@](C)(O)[C@H](O)C1
34	Bisacurone C	CC(C)=CC(=O)C[C@H](C)[C@@H]1C=C[C@@](C)(O)[C@H](O)C1
35	Bisacurone epoxide	CC(C)=CC(=O)C[C@H](C)[C@H]1C[C@H](O)[C@@](C)(O)[C@H]2O[C@@H]12

Table 3. Antifungal data of *Curcuma xanthorrhiza* based on PASS Online analysis

Nu	Compound	Antifungal (Probability of Being Active Percentage)
1	1,8-Cineol	0,214
2	alpha-Pinene	0,439
3	beta-Pinene	0,225
4	(+)-Camphor	0,27
5	Limonene	0,582
6	beta-Myrcene	0,584
7	alpha-Terpinolene	0,271
8	Curcumin	0,255
9	Borneol	0,448
10	Camphene	0,246
11	p-Cymene	0,368
12	beta-Caryophyllene	0,582

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Nu	Compound	Antifungal (Probability of Being Active Percentage)
13	(R)-(-)-Xanthorrhizol	0,59
14	beta-Curcumene	0,578
15	(+)-beta-Atlantone	0,635
16	Germacrone	0,26
17	Curzerenone	0,576
18	Humulene epoxide	0,507
19	(-)-beta-Caryophyllene epoxide	0,647
20	(E)-beta-Ocimene	0,573
21	4-Terpineol	0,466
22	alpha-Terpineol	0,435
23	Bisacumol	0,577
24	Bisacurone	0,767
25	Demethoxycurcumin	0,503
26	Isoborneol	0,448
27	1,3(15),10-Bisabolatrien-9-ol	0,67
28	3'-Demethoxycyclocurcumin	0,523
29	BHMH	0,453
30	Alnustone	0,473
31	DHBMH	0,517
32	Bisacurone A	0,767
33	Bisacurone B	0,767
34	Bisacurone C	0,767
35	Bisacurone epoxide	0,729

Table 4a. *In silico* SwissADME data supporting the antifungal activity of *Curcuma xanthorrhiza* against oil palm fungi

Nu	Compound	Water Solubility		Lipophilicity (Log P)	Bioavailability Score
		Log S (ESOL)	Class	Consensus Log P o/w	
1	1,8-Cineol	-2.52	Soluble	-	0.55
2	alpha-Pinene	-3.51	Soluble	-	0.55
3	beta-Pinene	-3.31	Soluble	-	0.55
4	(+)-Camphor	-2.16	Soluble	-	0.55
5	Limonene	-3.50	Soluble	-	0.55
6	beta-Myrcene	-3.05	Soluble	-	0.55
7	alpha-Terpinolene	-3.50	Soluble	-	0.55
8	Curcumin	-4.50	Moderately soluble	-	0.56
9	Borneol	-2.51	Soluble	-	0.55
10	Camphene	-3.34	Soluble	-	0.55
11	p-Cymene	-3.63	Soluble	-	0.55
12	beta-Caryophyllene	-3.87	Soluble	-	0.55
13	(R)-(-)-Xanthorrhizol	-4.65	Moderately soluble	-	0.55

Nu	Compound	Water Solubility		Lipophilicity (Log P)	Bioavailability Score
		Log S (ESOL)	Class	Consensus Log P o/w	
14	beta-Curcumene	-4.92	Moderately soluble	-	0.55
15	(+)-beta-Atlantone	-4.25	Moderately soluble	-	0.55
16	Germacrone	-3.37	Soluble	-	0.55
17	Curzerenone	-3.90	Moderately Soluble	-	0.55
18	Humulene epoxide	-3.67	Soluble	-	0.55
19	(-)-beta-Caryophyllene epoxide	-6.82	Soluble	-	0.55
20	(E)-beta-Ocimene	-3.17	Soluble	-	0.55
21	4-Terpineol	-2.78	Soluble	-	0.55
22	alpha-Terpineol	-2.87	Soluble	-	0.55
23	Bisacumol	-3.78	Soluble	-	0.55
24	Bisacurone	-2.32	Soluble	-	0.55
25	Demethoxycurcumin	-3.92	Soluble	-	0.55
26	Isoborneol	-2.51	Soluble	-	0.55
27	1,3(15),10-Bisabolatrien-9-ol	-3.53	Soluble	-	0.55
28	3'-Demethoxycyclocurcumin	-3.94	Soluble	-	0.56
29	BHMH	-3.87	Soluble	-	0.55
30	Alnustone	-4.39	Moderately soluble	-	0.55
31	DHBMH	-3.16	Soluble	-	0.55
32	Bisacurone A	-2.32	Soluble	-	0.55
33	Bisacurone B	-2.32	Soluble	-	0.55
34	Bisacurone C	-2.32	Soluble	-	0.55
35	Bisacurone epoxide	-2.01	Soluble	-	0.55

Table 4b. *In silico* drug-likeness SwissADME data supporting the antifungal activity of *Curcuma xanthorrhiza* against oil palm fungi

Nu	Compound	Drug-likeness				
		Lipinski	Ghose	Veber	Egan	Muegge
1	1,8-Cineol	Yes	No	Yes	Yes	No
2	alpha-Pinene	Yes	No	Yes	Yes	No
3	beta-Pinene	Yes	No	Yes	Yes	No
4	(+)-Camphor	Yes	No	Yes	Yes	No
5	Limonene	Yes	No	Yes	Yes	No
6	beta-Myrcene	Yes	No	Yes	Yes	No
7	alpha-Terpinolene	Yes	No	Yes	Yes	No
8	Curcumin	Yes	Yes	Yes	Yes	Yes
9	Borneol	Yes	No	Yes	Yes	No
10	Camphene	Yes	No	Yes	Yes	No
11	p-Cymene	Yes	No	Yes	Yes	No
12	beta-Caryophyllene	Yes	Yes	Yes	Yes	No
13	(R)-(-)-Xanthorrhizol	Yes	Yes	Yes	Yes	No
14	beta-Curcumene	Yes	Yes	Yes	Yes	No
15	(+)-beta-Atlantone	Yes	Yes	Yes	Yes	No
16	Germacrone	Yes	Yes	Yes	Yes	No
17	Curzerenone	Yes	Yes	Yes	Yes	Yes
18	Humulene epoxide	Yes	Yes	Yes	Yes	No

Nu	Compound	Drug-likeness				
		Lipinski	Ghose	Veber	Egan	Muegge
19	(-)-beta-Caryophyllene epoxide	Yes	Yes	Yes	Yes	No
20	(E)-beta-Ocimene	Yes	No	Yes	Yes	No
21	4-Terpineol	Yes	No	Yes	Yes	No
22	alpha-Terpineol	Yes	No	Yes	Yes	No
23	Bisacumol	Yes	Yes	Yes	Yes	No
24	Bisacurone	Yes	Yes	Yes	Yes	Yes
25	Demethoxycurcumin	Yes	Yes	Yes	Yes	Yes
26	Isoborneol	Yes	No	Yes	Yes	No
27	1,3(15),10-Bisabolatrien-9-ol	Yes	No	Yes	Yes	No
28	3'-Demethoxycyclocurcumin	Yes	Yes	Yes	Yes	Yes
29	BHMH	Yes	Yes	Yes	Yes	Yes
30	Alnustone	Yes	Yes	Yes	Yes	Yes
31	DHBMH	Yes	Yes	Yes	Yes	Yes
32	Bisacurone A	Yes	Yes	Yes	Yes	Yes
33	Bisacurone B	Yes	Yes	Yes	Yes	Yes
34	Bisacurone C	Yes	Yes	Yes	Yes	Yes
35	Bisacurone epoxide	Yes	Yes	Yes	Yes	Yes

Table 4c. *In silico* physicochemical properties SwissADME data supporting the antifungal activity of *Curcuma xanthorrhiza* against oil palm fungi

Nu	Compound	Physicochemical Properties								
		Mol weight(g/mol)	Num. heavy atoms	Num. arom heavy atoms	Fraction Csp3	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors	Molar Refractivity	TPSA (A^2)
1	1,8-Cineol	154.25	11	0	1.00	0	1	0	47.12	9.23
2	alpha-Pinene	136.23	10	0	0.80	0	0	0	45.22	0.00
3	beta-Pinene	136.23	10	0	0.80	0	0	0	45.22	0.00
4	(+)-Camphor	152.23	11	0	0.90	0	1	0	45.64	17.07
5	Limonene	136.23	10	0	0.60	1	0	0	47.12	0.00
6	beta-Myrcene	136.23	10	0	0.40	4	0	0	48.76	0.00
7	alpha-Terpinolene	136.23	10	0	0.60	0	0	0	47.12	0.00
8	Curcumin	368.38	27	12	0.10	7	6	3	103.70	96.22
9	Borneol	154.25	11	0	1.00	0	1	1	46.60	20.23
10	Camphene	136.23	11	0	0.80	0	0	0	45.22	0.00
11	p-Cymene	134.22	10	6	0.40	1	0	0	45.99	0.00
12	beta-Caryophyllene	204.35	15	0	0.73	0	0	0	68.78	0.00
13	(R)-(-)-Xanthorrhizol	218.33	16	6	0.47	4	1	1	71.57	20.23
14	beta-	204.35	15	0	0.60	4	0	0	70.68	0.00

Nu	Compound	Physicochemical Properties								
		Mol weight(g/mol)	Num. heavy atoms	Num. arom heavy atoms	Fraction Csp3	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors	Molar Refractivity	TPSA (A^2)
15	Curcumene (+)-beta-Atlantone	218.33	16	0	0.53	4	1	0	70.88	17.07
16	Germacrone	218.33	16	0	0.53	0	1	0	70.88	17.07
17	Curzerenone	230.30	17	5	0.40	2	2	0	69.16	30.21
18	Humulene epoxide	220.35	16	0	0.73	0	1	0	69.91	12.53
19	(-)-beta-Caryophyllene epoxide	220.35	16	0	0.87	0	1	0	68.27	12.53
20	(E)-beta-Ocimene	136.23	10	0	0.40	3	0	0	48.76	0.00
21	4-Terpineol	154.25	11	0	0.80	1	1	1	48.80	20.23
22	alpha-Terpineol	154.25	11	0	0.80	1	1	1	48.80	20.23
23	Bisacumol	218.33	16	6	0.47	4	1	1	70.71	20.23
24	Bisacurone	252.35	18	0	0.67	4	3	2	73.72	57.53
25	Demethoxycurcumin	338.35	25	12	0.10	7	5	2	96.31	83.83
26	Isoborneol	154.25	11	0	1.00	0	1	1	46.60	20.23
27	1,3(15),10-Bisabolatrien-9-ol	220.35	16	0	0.60	4	1	1	71.84	20.23
28	3'-Demethoxycyclocurcumin	338.35	25	12	0.15	4	5	2	94.29	75.99
29	BHMH	376.44	27	12	0.43	10	6	4	104.09	99.38
30	Alnustone	262.35	20	12	0.11	6	1	0	84.78	17.07
31	DHBMH	386.40	28	12	0.24	9	7	3	103.65	113.29
32	Bisacurone A	252.35	18	0	0.67	4	3	2	73.72	57.53
33	Bisacurone B	252.35	18	0	0.67	4	3	2	73.72	57.53
34	Bisacurone C	252.35	18	0	0.67	4	3	2	73.72	57.53
35	Bisacurone epoxide	268.35	19	0	0.80	4	4	2	73.16	70.06

Table 5. In silico data of *Curcuma xanthorrhiza* from pkCSM

Nu	Compound	AMES	Hepatotoxicity	Environmental Toxicity

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		Toxicity		T.Pyriformis toxicity (log ug/L)	Minnow toxicity (log Mm)
1	1,8-Cineol	No	No	0.171	1.735
2	alpha-Pinene	No	No	0.45	1.159
3	beta-Pinene	No	No	0.633	1.131
4	(+)-Camphor	No	No	0.267	1.34
5	Limonene	No	No	0.579	1.203
6	beta-Myrcene	No	No	0.925	0.646
7	alpha-Terpinolene	No	No	0.52	1.215
8	Curcumin	No	No	0.372	-0.631
9	Borneol	No	No	0.199	1.608
10	Camphene	No	No	0.533	1.19
11	p-Cymene	No	No	0.726	0.654
12	beta-Caryophyllene	No	No	1.409	0.413
13	(R)-(-)-Xanthorrhizol	No	No	2.429	-0.191
14	beta-Curcumene	No	No	1.935	0.023
15	(+)-beta-Atlantone	No	No	1.696	0.488
16	Germacrone	No	No	1.423	0.801
17	Curzerenone	No	No	1.966	0.316
18	Humulene epoxide	No	No	1.09	1.194
19	(-)-beta-Caryophyllene epoxide	No	No	1.073	1.049
20	(E)-beta-Ocimene	No	No	0.825	0.694
21	4-Terpineol	No	No	0.36	1.576
22	alpha-Terpineol	No	No	0.008	1.8
23	Bisacumol	No	No	1.616	0.13
24	Bisacurone	No	No	0.61	1.665
25	Demethoxycurcumin	No	No	0.488	-0.647
26	Isoborneol	No	No	0.199	1.608
27	1,3(15),10-Bisabolatrien-9-ol	No	No	1.719	0.612
28	3'-Demethoxycyclocurcumin	No	No	0.852	0.077
29	BHMH	No	Yes	0.346	-0.092
30	Alnustone	No	Yes	1.201	-0.962
31	DHBMH	No	No	0.299	-0.533
32	Bisacurone A	No	No	0.61	1.665
33	Bisacurone B	No	No	0.61	1.665
34	Bisacurone C	No	No	0.61	1.665
35	Bisacurone epoxide	Yes	No	0.315	1.623

Analysis and Discussion of the Antifungal Data of *Curcuma xanthorrhiza* Based on PASS Online

Curcuma xanthorrhiza demonstrated strong antifungal potential based on PASS Online predictions. The probability of activity (Pa) indicates the likelihood of biological activity, with values closer to 1 reflecting greater antifungal potential. Table 3 showed that oxygenated sesquiterpenes and curcuminoid derivatives generally exhibited higher Pa values than simple monoterpenes. The highest Pa value (0.767) was recorded for Bisacurone, Bisacurone A, B, and C, indicating that these compounds are the principal antifungal candidates in Java turmeric. Their

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oxygenated sesquiterpene structures are predicted to disrupt fungal plasma membranes, increase membrane permeability, and inhibit fungal metabolism and hyphal growth.

Bisacurone epoxide also showed high predicted activity (Pa = 0.729). The epoxide group enhances biological reactivity by interacting with fungal proteins and enzymes, inducing oxidative stress, and inhibiting fungal cell wall formation and reproduction. Other promising compounds included (-)-β-caryophyllene epoxide (Pa = 0.647) and (+)-β-atlantone (Pa = 0.635). These oxygenated sesquiterpenes are predicted to inhibit fungal biofilm formation and damage membrane lipids, while their higher polarity promotes stronger interactions with microbial membranes.

Xanthorrhizol (Pa = 0.590) also exhibited considerable antifungal potential. This phenolic compound acts by denaturing membrane proteins, inhibiting ergosterol biosynthesis, and increasing ion leakage, providing broad-spectrum antifungal activity against Candida species and several phytopathogenic fungi. Monoterpenes such as limonene (0.582), β-myrcene (0.584), and borneol (0.448) displayed moderate antifungal activity. Although their lipophilic nature enables penetration across membranes, their smaller molecular size and simpler structures likely explain their lower activity compared with sesquiterpenes.

Curcumin exhibited the lowest predicted activity (Pa = 0.255), but it may contribute through synergistic interactions with other phenolic and terpenoid compounds. Its antifungal effects are associated with inhibition of spore formation, mitochondrial dysfunction, and increased reactive oxygen species (ROS), while its lower PASS value may reflect limited bioavailability. Overall, PASS Online analysis indicates that the antifungal activity of Curcuma xanthorrhiza is mainly associated with oxygenated sesquiterpenes, particularly bisacurone derivatives, β-caryophyllene epoxide, and xanthorrhizol. These compounds represent promising candidates for the development of environmentally friendly natural biofungicides applicable in agriculture and healthcare.

Analysis and Discussion of In Silico SwissADME Data Supporting the Antifungal Activity of *Curcuma xanthorrhiza* Against Fungi in Oil Palm Plants

SwissADME analysis indicated that most bioactive compounds from Curcuma xanthorrhiza exhibit physicochemical properties that support their development as natural antifungal agents. Parameters including water solubility, lipophilicity (Log P), and bioavailability influence membrane penetration, chemical stability, and distribution within oil palm tissues. Most compounds were classified as soluble, indicating good water solubility that facilitates formulation and absorption on plant surfaces. Compounds such as 1,8-cineole, borneol, bisacurone, and bisacurone epoxide exhibited favorable Log S values, suggesting effective dispersion in plant tissues and improved inhibition of fungal spore germination and hyphal growth.

Monoterpenes, including α-pinene, β-pinene, limonene, and β-myrcene, also showed good solubility (Log S approximately −3 to -3.5). Their volatility and moderate hydrophobicity facilitate penetration into fungal membranes, resulting in membrane disruption, ion leakage, and damage to lipid structures. Curcumin, xanthorrhizol, β-curcumene, and alnustone were

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categorized as moderately soluble, but their higher lipophilicity favors penetration into ergosterol-rich fungal membranes, contributing to membrane instability and fungal cell lysis.

Oxygenated sesquiterpenes, including humulene epoxide, β-caryophyllene epoxide, curzerenone, and bisacurone epoxide, combined favorable solubility with high biological activity. Their epoxide groups enhance interactions with fungal proteins and enzymes, disrupt plasma membranes, and inhibit fungal metabolism, making them promising plant-derived antifungal compounds. Nearly all compounds exhibited bioavailability scores of 0.55–0.56, indicating good absorption and stability in biological systems. These consistent values suggest that the secondary metabolites of Curcuma xanthorrhiza have strong potential as biological control agents against pathogenic fungi in oil palm.

Among all metabolites, the bisacurone group showed the greatest promise. Bisacurone, Bisacurone A, B, C, and bisacurone epoxide combined favorable solubility, stable bioavailability, and high predicted antifungal activity, supporting their development as active ingredients in natural biofungicides. Overall, the SwissADME analysis demonstrated that the secondary metabolites of Curcuma xanthorrhiza exhibit physicochemical characteristics favorable to antifungal activity. The complementary properties of monoterpenes, oxygenated sesquiterpenes, and phenolic compounds may provide synergistic effects, supporting the use of Java turmeric as an environmentally friendly biofungicide for controlling fungal diseases in oil palm cultivation.

Analysis and Discussion of In Silico Drug-Likeness Data from SwissADME Supporting the Antifungal Activity of *Curcuma xanthorrhiza* Against Fungi in Oil Palm Plants

Drug-likeness analysis using SwissADME showed that most secondary metabolites of *Curcuma xanthorrhiza* exhibit physicochemical properties that support their development as natural antifungal agents. The evaluation was performed using the Lipinski, Ghose, Veber, Egan, and Muegge rules, which are widely used to assess the suitability of bioactive compounds for drug and natural biofungicide development (da Silva *et al*., 2026). All analyzed compounds satisfied Lipinski's rule, indicating favorable molecular size, hydrogen-bonding capacity, and lipophilicity, which support absorption, permeability, and interactions with fungal membranes. These results suggest that the secondary metabolites of Java turmeric have good potential as natural antifungal agents against oil palm pathogens (Jenner *et al*., 2011).

Several monoterpenes, including 1,8-cineole, α-pinene, β-pinene, limonene, and camphene, did not satisfy the Ghose and Muegge criteria because of their relatively small molecular size and high volatility. Nevertheless, these compounds remain biologically active by disrupting fungal plasma membranes and increasing membrane permeability, leading to leakage of intracellular components (Leiva-Mora *et al*., 2025). The most favorable compounds were curcumin, curzerenone, bisacurone, demethoxycurcumin, alnustone, and other bisacurone derivatives, as they fulfilled all evaluated drug-likeness parameters. Their balanced molecular size, flexibility, polarity, and lipophilicity indicate greater stability and stronger interactions with fungal target proteins (Oliveira *et al*., 2015).

Curcumin and its derivatives exert antifungal activity by inhibiting ergosterol biosynthesis and disrupting oxidative metabolism. Their phenolic groups and heptadienone chains further

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enhance interactions with fungal membranes and proteins, enabling inhibition of several phytopathogenic fungi, including Fusarium, Aspergillus, and *Candida* spp. (Chen *et al*., 2018). Oxygenated sesquiterpenes, including humulene epoxide, β-caryophyllene epoxide, and bisacurone epoxide, also demonstrated favorable drug-likeness properties. Their epoxide groups increase biological reactivity, inhibit fungal cell wall biosynthesis, induce oxidative stress, and suppress hyphal growth (Li *et al*., 2022).

Among all compounds, the bisacurone group emerged as the most promising candidate. Bisacurone A, B, and C, and bisacurone epoxide, met all Lipinski, Ghose, Veber, Egan, and Muegge criteria while also exhibiting high predicted antifungal activity and favorable biological compatibility. These combined findings support bisacurone as one of the most promising metabolites of Curcuma xanthorrhiza for development as a natural biofungicide against fungal diseases in oil palm. Overall, the drug-likeness analysis indicates that most secondary metabolites of Curcuma xanthorrhiza exhibit physicochemical characteristics conducive to natural antifungal development. Compounds that satisfy all drug-likeness criteria are expected to exhibit improved absorption, distribution, and biological interactions, thereby supporting the use of Java turmeric as a sustainable and environmentally friendly biofungicide (da Silva *et al*., 2026; Jenner *et al*., 2011; Oliveira *et al*., 2015).

Analysis and Discussion of In Silico Physicochemical Properties Data from SwissADME Supporting the Antifungal Activity of *Curcuma xanthorrhiza* Against Fungi in Oil Palm Plants

The physicochemical analysis using SwissADME demonstrated that the secondary metabolites of Curcuma xanthorrhiza exhibit properties conducive to natural antifungal activity. Parameters including molecular weight, heavy atoms, fraction Csp3, rotatable bonds, hydrogen bond donors and acceptors, molar refractivity, and Topological Polar Surface Area (TPSA) are important determinants of compound interactions with fungal membranes and biological targets (Pratama *et al*., 2025). Most monoterpenes, including 1,8-cineole, α-pinene, β-pinene, limonene, and α-terpinolene, exhibited relatively low molecular weights (136–154 g/mol), facilitating diffusion through fungal membranes and enhancing membrane disruption and intracellular ion leakage (Shahina *et al*., 2022). In addition, compounds such as 1,8-cineole, borneol, and isoborneol showed high fraction Csp3 values, indicating greater structural flexibility and improved interactions with fungal target proteins (Cox *et al*., 2020).

Curcuminoids, including curcumin, demethoxycurcumin, and 3′-demethoxycyclocurcumin, possessed relatively high TPSA values and multiple hydrogen bond acceptors, enabling stronger interactions with fungal proteins involved in ergosterol biosynthesis and membrane function (Anukanon *et al*., 2025). However, excessively high TPSA, as observed in 1,5-dihydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-4,6-heptadien-3-one (113.29 Å²), may reduce membrane permeability despite maintaining strong biological interactions, highlighting the importance of balancing polarity and lipophilicity (Clark, 1999).

Sesquiterpenes such as β-caryophyllene, β-curcumene, humulene epoxide, and β-caryophyllene epoxide exhibited low to moderate TPSA values and relatively few rotatable

bonds, indicating hydrophobicity and structural stability. These characteristics facilitate direct interaction with fungal membrane lipids, leading to membrane damage and inhibition of hyphal growth, while epoxide groups further enhance reactivity toward fungal proteins (Sotto *et al*., 2023).

The bisacurone group demonstrated the most balanced physicochemical profile. Bisacurone and its derivatives possessed moderate molecular weights, flexible rotatable bonds, and TPSA values of approximately 57–70 Å², providing an optimal balance between membrane permeability and interaction with biological targets (Anjum *et al*., 2026). Their balanced hydrogen-bond donor and acceptor capacities also favor interactions with enzymes involved in fungal cell wall formation and ergosterol biosynthesis, thereby contributing to stronger antifungal activity than that of non-oxygenated terpenes (Li *et al*., 2022). Overall, the physicochemical analysis indicates that the secondary metabolites of *Curcuma xanthorrhiza*, particularly bisacurone derivatives, curcuminoids, and oxygenated sesquiterpenes, exhibit molecular characteristics consistent with effective antifungal activity. Their balanced molecular weight, TPSA, structural flexibility, and hydrogen-bonding capacity make them promising candidates for developing environmentally friendly, sustainable biofungicides against oil palm-pathogenic fungi.

Analysis and Discussion of In Silico Toxicity Data of *Curcuma xanthorrhiza* Based on PKCSM as Support for Antifungal Activity in Oil Palm Plants

The PKCSM analysis indicated that most secondary metabolites of Curcuma xanthorrhiza possess relatively safe toxicity profiles, supporting their potential as natural antifungal agents for oil palm disease management. Toxicity assessment included AMES toxicity, hepatotoxicity, Tetrahymena pyriformis toxicity, and Minnow toxicity, which are important parameters for evaluating the safety of biofungicides toward non-target organisms and the environment (Devaraj *et al*., 2014). Most compounds were predicted to be non-mutagenic (AMES-negative), suggesting a low risk of genetic damage and supporting their safe application as environmentally friendly, plant-derived antifungal agents (Salleh *et al*., 2016). An exception was bisacurone epoxide, which showed positive AMES toxicity. This result is likely related to the presence of a reactive epoxide group, although further in vitro and in vivo studies are required, as in silico predictions do not always reflect actual biological toxicity (Gomes *et al*., 2020).

For hepatotoxicity, nearly all compounds were predicted to be non-hepatotoxic, except 1,7-Bis(4-hydroxy-3-methoxyphenyl)-3,5-heptanediol and alnustone, which may pose hepatotoxic risks. These findings indicate that compounds with larger molecular size and multiple hydroxyl groups should receive additional safety evaluation before large-scale agricultural application (Pratama *et al*., 2025). Environmental toxicity analysis based on Tetrahymena pyriformis showed that compounds such as xanthorrhizol, curzerenone, and β-curcumene exhibited relatively favorable toxicity values, indicating lower environmental risks than conventional synthetic fungicides and supporting their use as environmentally friendly antifungal agents (Khafagy *et al*., 2026). In the Minnow toxicity assessment, curcumin, demethoxycurcumin, and alnustone exhibited relatively high toxicity to aquatic organisms,

suggesting that formulation and application rates should be carefully optimized to minimize ecological impacts. In contrast, α-terpineol, bisacurone, and borneol exhibited more favorable toxicity profiles, indicating greater safety for aquatic environments (Aptula *et al*., 2005). The monoterpene group, including 1,8-cineole, limonene, α-pinene, and β-pinene, showed consistently low toxicity, being non-mutagenic, non-hepatotoxic, and environmentally safer. Their natural biodegradability further supports their potential as sustainable biofungicide components (Reyes-Ávila *et al*., 2025).

Similarly, the bisacurone group demonstrated highly favorable safety characteristics. Bisacurone, Bisacurone A, B, and C showed no predicted AMES toxicity or hepatotoxicity while maintaining acceptable environmental toxicity values. Combined with their strong predicted antifungal activity, these findings identify bisacurone derivatives as promising and safe candidates for biofungicide development. Overall, PKCSM analysis indicates that most secondary metabolites of *Curcuma xanthorrhiza* possess favorable toxicity profiles for biological and environmental safety. Bisacurone derivatives, monoterpenes, and several oxygenated sesquiterpenes represent the most promising natural biofungicide candidates, although compounds predicted to exhibit mutagenic or hepatotoxic potential require further experimental validation before field application (Devaraj *et al*., 2014; Salleh *et al*., 2016; Gomes *et al*., 2020; Pratama *et al*., 2025; Khafagy *et al*., 2026; Aptula *et al*., 2005; Reyes-Ávila *et al*., 2025).

CONCLUSION

Based on the *in silico* analysis results, *Curcuma xanthorrhiza* has high potential as a natural biofungicide against fungi in oil palm plants. Bisacurone compounds and their derivatives demonstrated the best antifungal activity, physicochemical characteristics, drug-likeness properties, and toxicity profiles. The combination of biological effectiveness and environmental safety supports the development of Java turmeric as an environmentally friendly and sustainable alternative fungicide.

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