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IN SILICO INVESTIGATION OF ANTIFUNGAL BIOACTIVE COMPOUNDS FROM *Areca catechu* SEEDS

INVESTIGASI IN SILICO SENYAWA BIOAKTIF ANTIJAMUR DARI BIJI PINANG *(Areca catechu)*

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Abstract

This study evaluated the antifungal potential of bioactive compounds present in betel nut seeds (*Areca catechu* L.) through an in silico approach. The assessment included prediction of antifungal activity (Pa), pharmacokinetic profiling using SwissADME, evaluation of physicochemical and drug-likeness properties, and toxicity prediction with pkCSM. The results indicated that betel nut seeds contain various bioactive constituents, including phenolic compounds, flavonoids, alkaloids, fatty acids, and proanthocyanidins, which may contribute to antifungal activity through different mechanisms. Among the analyzed compounds, proanthocyanidins showed the highest predicted antifungal activity, followed by arecoline and catechin. These compounds are expected to inhibit fungal growth by disrupting cell membrane integrity, reducing biofilm formation, and interfering with essential metabolic pathways. Pharmacokinetic analysis revealed that low-molecular-weight compounds, such as catechin, certain alkaloids, and fatty acids, generally exhibited greater solubility and drug-likeness, suggesting greater bioavailability. In contrast, larger polyphenolic compounds demonstrated lower absorption potential but may remain active through direct interactions with fungal cell surfaces. Toxicity predictions suggested that most compounds pose relatively low mutagenic risk, although some alkaloids may have hepatotoxic potential. Overall, the findings indicate that the antifungal properties of Areca catechu are likely attributable to the combined action of multiple bioactive compounds, highlighting its potential as a natural source for developing environmentally friendly antifungal agents.

Keywords: *Areca catechu; antifungi; in silico; SwissADME; PKCSM*

Abstrak

Penelitian ini bertujuan untuk mengevaluasi potensi antijamur senyawa bioaktif yang terkandung dalam biji pinang (*Areca catechu* L.) melalui pendekatan *in silico*. Analisis dilakukan dengan memprediksi aktivitas antijamur (Pa), profil farmakokinetik menggunakan SwissADME, evaluasi sifat fisikokimia dan *drug-likeness*, serta prediksi toksisitas menggunakan pkCSM. Hasil penelitian menunjukkan bahwa biji pinang mengandung berbagai senyawa bioaktif, seperti fenolik, flavonoid, alkaloid, asam lemak, dan proantosianidin yang berpotensi berperan dalam aktivitas antijamur melalui mekanisme yang berbeda. Di antara senyawa yang dianalisis, proantosianidin menunjukkan nilai prediksi aktivitas antijamur tertinggi, diikuti oleh arekolin dan katekin. Senyawa-senyawa tersebut diperkirakan mampu menghambat pertumbuhan jamur melalui gangguan terhadap integritas membran sel, penghambatan pembentukan biofilm, serta interferensi terhadap jalur metabolisme yang penting. Analisis farmakokinetik menunjukkan bahwa senyawa dengan bobot molekul lebih rendah, seperti katekin, beberapa alkaloid, dan asam lemak, memiliki karakteristik kelarutan dan *drug-likeness* yang lebih baik sehingga berpotensi memiliki

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bioavailabilitas yang lebih tinggi. Sebaliknya, senyawa polifenol berukuran besar cenderung memiliki kemampuan absorpsi yang lebih rendah, tetapi tetap berpotensi aktif melalui interaksi langsung dengan permukaan sel jamur. Prediksi toksisitas menunjukkan bahwa sebagian besar senyawa memiliki risiko mutagenisitas yang rendah, meskipun beberapa alkaloid berpotensi menimbulkan efek hepatotoksik. Secara keseluruhan, aktivitas antijamur *Areca catechu* diduga berasal dari kerja sinergis berbagai senyawa bioaktif, sehingga tanaman ini berpotensi dikembangkan sebagai sumber agen antijamur alami yang efektif dan ramah lingkungan.

Kata Kunci : Areca catechu; antijamur; in silico; SwissADME; PKCSM

INTRODUCTION

Indonesia is one of the world's biodiversity-rich countries, possessing numerous plant species with potential as sources of bioactive compounds. Among them, betel nut (*Areca catechu* L.) has long been utilized in traditional medicine and cultural practices throughout Southeast Asia. Previous studies have shown that betel nut seeds contain various secondary metabolites, including alkaloids, flavonoids, tannins, proanthocyanidins, and fatty acids, which exhibit antimicrobial and antifungal activities (Ali & Khuwaja, 2011).

Fungal diseases remain a major challenge in agriculture because they can significantly reduce crop productivity and quality. In plantation crops such as oil palm, pathogenic fungi infect roots, stems, and leaves, disrupting essential physiological processes. Although synthetic fungicides are widely used to control these pathogens, their prolonged application may lead to fungal resistance, chemical residues, and environmental contamination (El-Baky & Amara, 2021). Consequently, there is growing interest in identifying natural, environmentally friendly alternatives for managing fungal diseases.

Several bioactive compounds from *Areca catechu* have demonstrated promising antifungal properties. Polyphenolic compounds, particularly catechins and proanthocyanidins, are reported to inhibit fungal growth by disrupting cell membrane integrity, suppressing biofilm formation, and interfering with essential enzymatic activities (Rauf *et al*., 2019). In addition, alkaloids such as arecoline, arecaidine, guvacine, and guvacoline exhibit antimicrobial activity through membrane disruption and metabolic interference (Sun *et al*., 2024). Fatty acids, including lauric, myristic, and oleic acids, have also been associated with antifungal effects by damaging fungal lipid membranes and inducing cellular leakage (Zouine *et al*., 2024). The diversity of these compounds suggests that *Areca catechu* represents a promising source of natural antifungal agents.

Recent advances in computational chemistry have enabled the application of in silico approaches to evaluate bioactive compounds. Tools such as SwissADME and pkCSM enable the prediction of pharmacokinetic behavior, physicochemical characteristics, drug-likeness, and toxicity profiles without extensive laboratory experimentation (Shaker *et al*., 2021). SwissADME provides information on solubility, lipophilicity, bioavailability, and compliance with drug-likeness criteria, whereas pkCSM predicts toxicity-related parameters, including mutagenicity and hepatotoxicity. These analyses are valuable for identifying compounds with favorable biological activity and safety profiles z (Lindner *et al*., 2026; Leka *et al*., 2026).

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In oil palm cultivation, fungal pathogens such as *Ganoderma boninense* cause severe economic losses due to basal stem rot. Therefore, sustainable disease management strategies are urgently needed. Previous studies have reported that extracts of *Areca catechu* exhibit antifungal activity against several pathogenic fungi, suggesting that its bioactive compounds may serve as potential candidates for natural biofungicide development (Kang *et al*., 2026; Qiao *et al*., 2026).

However, the effectiveness of antifungal compounds depends not only on biological activity but also on physicochemical, pharmacokinetic, and toxicity characteristics. Therefore, a comprehensive *in silico* evaluation of bioactive compounds from *Areca catechu* is necessary. This study aims to analyze their antifungal activity, drug-likeness, physicochemical properties, pharmacokinetic behavior, and toxicity profiles to identify promising candidates for the development of effective, environmentally friendly antifungal agents.

RESEARCH METHODS

1. Type of Research

This study employed a descriptive in silico approach to analyze the potential of bioactive compounds from betel nut (*Areca catechu*) seeds as antifungal agents. The in silico method was utilized to evaluate the physicochemical, pharmacokinetic, drug-likeness, and toxicity properties of selected compounds without direct laboratory experimentation. This approach has become increasingly important in modern drug discovery because it enables rapid and cost-effective screening of bioactive compounds while providing preliminary predictions of their biological activities (Lin *et al*., 2020).

2. Data Sources

The data used in this study consisted of secondary data obtained from scientific literature and publicly accessible chemical databases. Bioactive compounds reported in *Areca catechu* seeds, including alkaloids, flavonoids, phenolic compounds, proanthocyanidins, and fatty acids, were selected for analysis. Information on the chemical structures of these compounds was obtained from the PubChem database as Simplified Molecular Input Line Entry System (SMILES) notation. The selection of compounds was supported by metabolomic studies that reported a wide diversity of metabolites in *Areca catechu* seeds, including numerous phenolic compounds, alkaloids, and lipid-derived metabolites (Lai *et al*., 2023).

3. Analytical Tools and Platforms

Several computational platforms were employed in this study. SwissADME was used to evaluate the pharmacokinetic properties and drug-likeness of the selected compounds through parameters such as lipophilicity (LogP), water solubility (LogS), bioavailability score, and compliance with Lipinski, Veber, Ghose, Egan, and Muegge rules (Daina *et al*., 2017). Toxicity prediction was performed using pkCSM, which provided information regarding Ames mutagenicity, hepatotoxicity, and environmental toxicity based on fish and protozoan models (Pires *et al*., 2015). Additionally, the PubChem database was used to obtain two-dimensional

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(2D) and three-dimensional (3D) molecular structures for use as input in computational analyses (Bolton *et al*., 2008).

4. Research Procedure

The research was conducted through several sequential stages. Initially, bioactive compounds from *Areca catechu* seeds were identified based on published metabolomic studies and phytochemical reviews. The chemical structures of the selected compounds were then retrieved from the PubChem database in SMILES format. Subsequently, pharmacokinetic properties and drug-likeness were evaluated using SwissADME, including parameters such as lipophilicity, water solubility, and bioavailability, as well as rule-based drug-likeness criteria. Toxicity assessments were performed using pkCSM to predict mutagenicity, hepatotoxicity, and environmental toxicity.

All generated data were compiled and organized into comparative tables for analysis. Finally, the results were interpreted to identify compounds with favorable pharmacokinetic profiles, acceptable bioavailability, and low toxicity, indicating their potential as antifungal candidates.

5. Data Analysis Technique

Data analysis was conducted using a descriptive-comparative approach. The selected compounds were evaluated and compared based on reported antifungal activities in the literature, as well as their ADME profiles, drug-likeness, and predicted toxicity. This analytical framework integrates phytochemical data with in silico predictions to support the identification of potential natural bioactive compounds for further development as antifungal agents (Khanzada *et al*., 2021).

6. Compound Selection Criteria

The selection of potential antifungal compounds was based on several predefined criteria. Compounds were considered promising candidates if they exhibited reported biological activity, particularly in the phenolic and alkaloid groups. In addition, selected compounds were required to comply with at least two drug-likeness rules, exhibit a bioavailability score of ≥ 0.55, show negative Ames toxicity predictions, and present low hepatotoxicity risk (Khanzada *et al*., 2021).

7. Research Outputs

The expected outcomes of this study include the classification of bioactive compounds present in *Areca catechu* seeds, comprehensive ADME and toxicity profiles of the analyzed compounds, identification of major compounds with potential antifungal activity, and an overall assessment of the feasibility of developing natural biofungicides derived from betel nut (*Areca catechu*).

RESULTS AND DISCUSSION

Table 1. Structural images of compounds from the Areca plant (*Areca catechu*).

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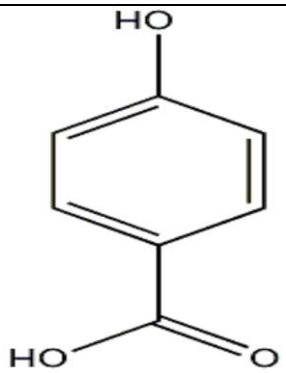
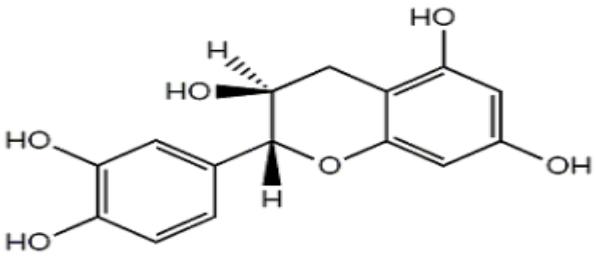
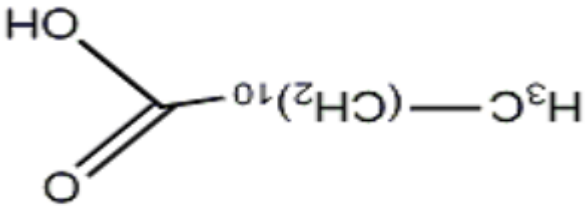
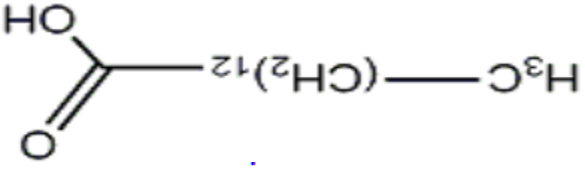
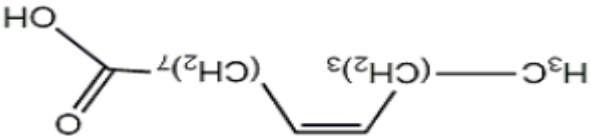
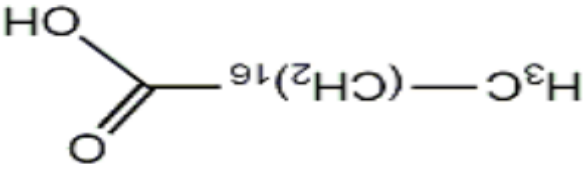
Nu	Coumpound	Chemical Structure
1	4-hydroxybenzoic acid (4-HBA)	
2	(+)-Catechin	
3	Lauric acid	
4	Myristic acid	
5	Myristoleic acid	
6	Octadecanoic acid	

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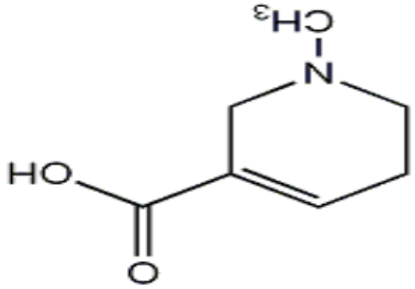
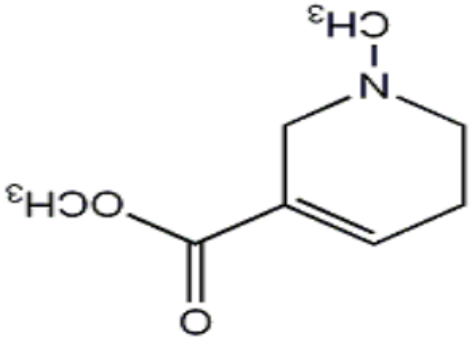
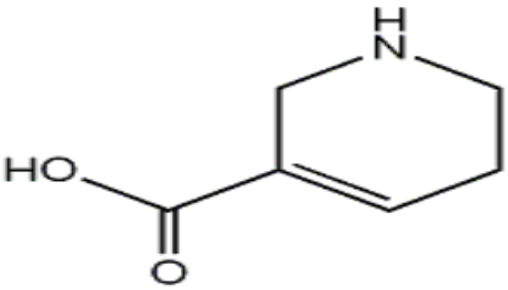
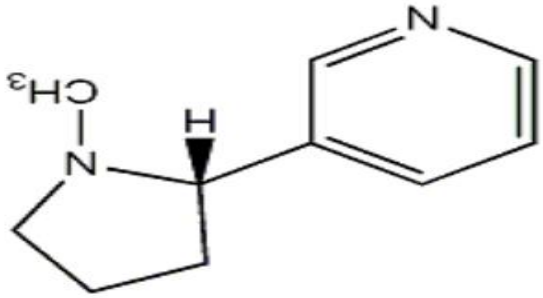
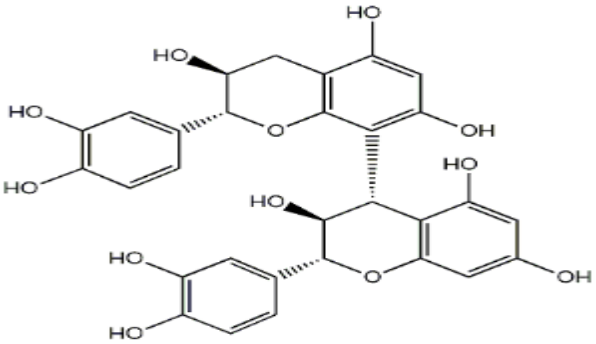
7	Arecaidine	
8	Arecoline	
9	Guvacine	
10	Nicotine	
11	Procyanidin B3	

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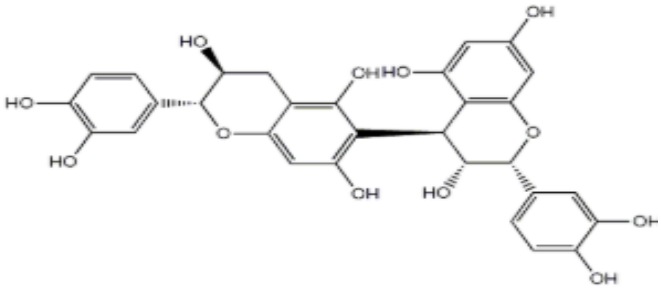
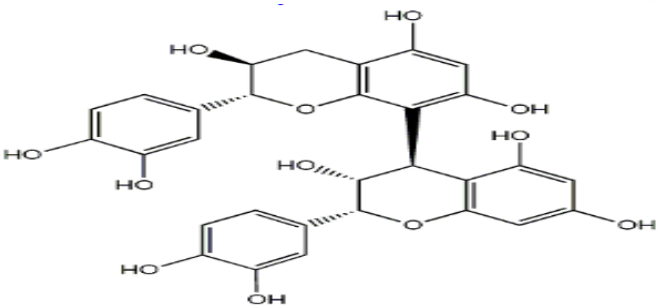
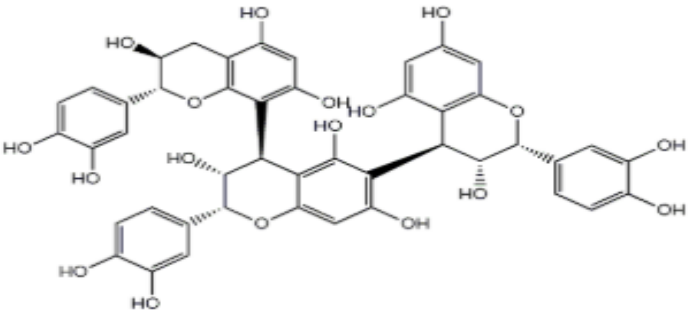
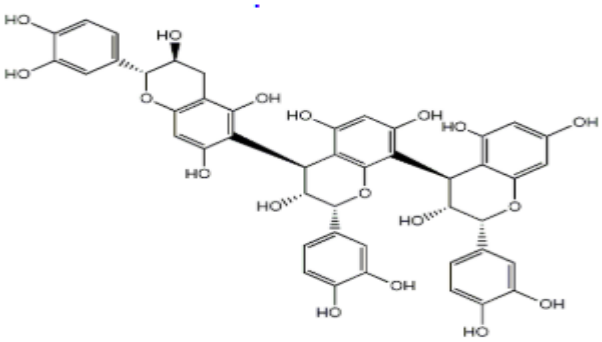
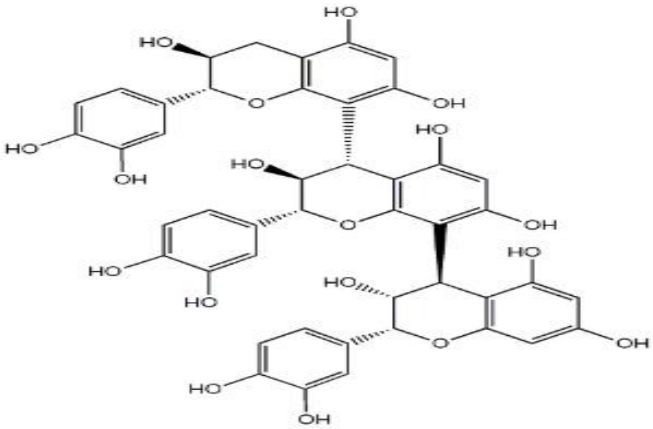
12	Procyanidin B7	
13	Procyanidin B1	
14	Epicatechin-(4beta→6)-epicatechin-(4beta→8)-catechin (EEC)	
15	Arecatannin B1	
16	Procyanidin C4	

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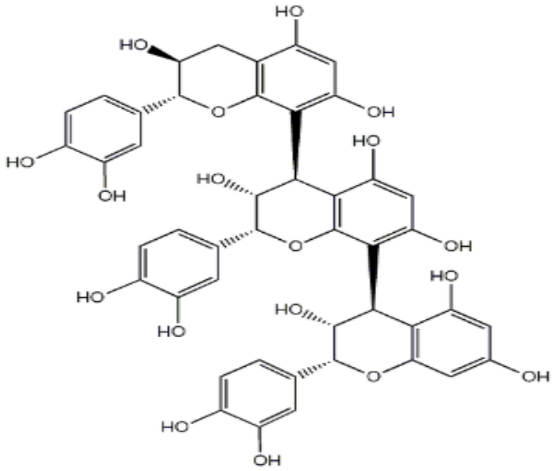
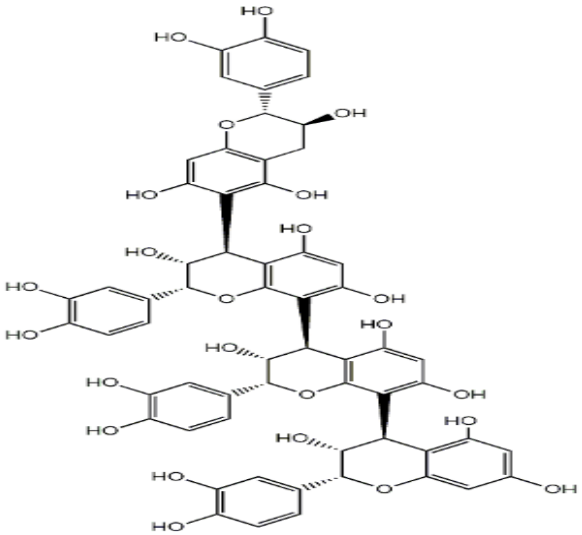
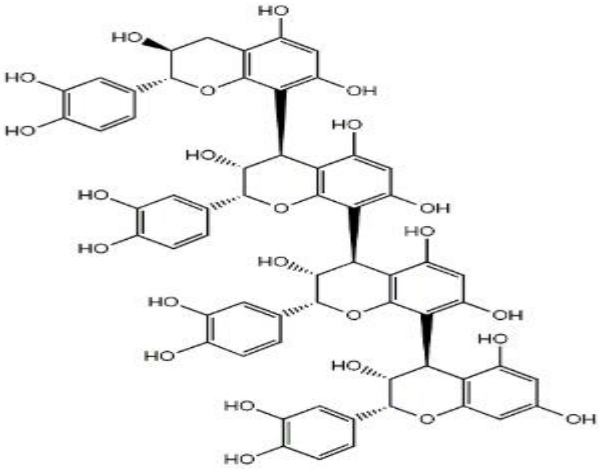
17	Arecatannin A1	
18	[Epicatechin-(4beta→8)]2-epicatechin-(4beta→6)-catechin (EEEC)	
19	Arecatannin A2	

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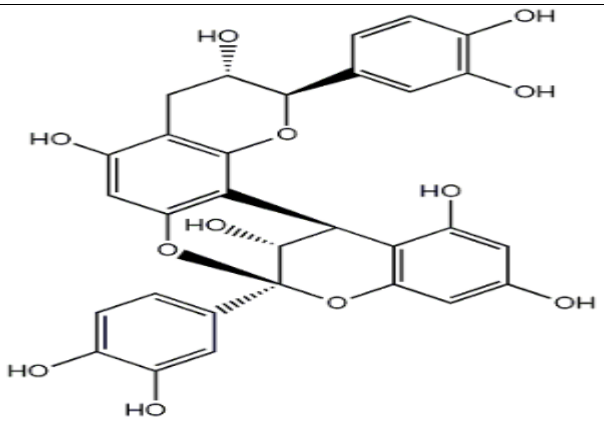
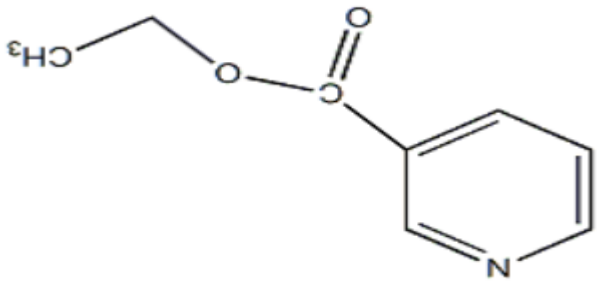
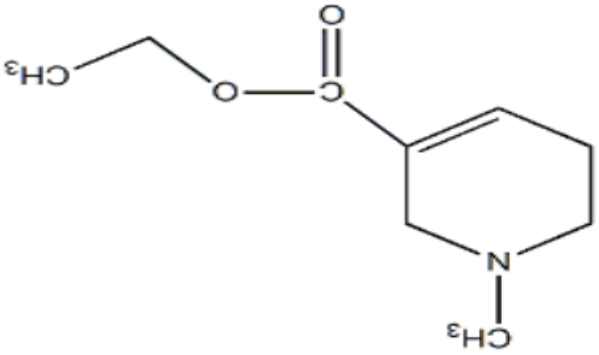
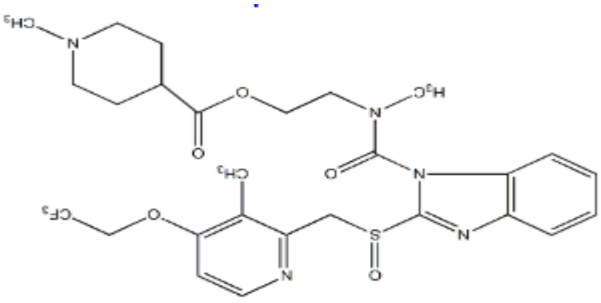
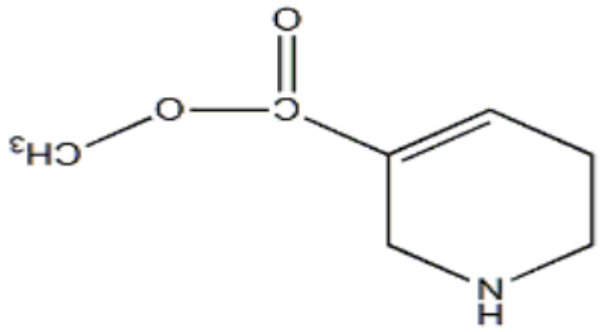
20	Proanthocyanidin A1	
21	Ethyl nicotinate	
22	Ethyl N-methyl-1,2,5,6-tetrahydro-pyridine-3-carboxylate (ENTPC)	
23	Ethyl N-methylpiperidine-3-carboxylate (ENPC)	
24	Guvacoline	

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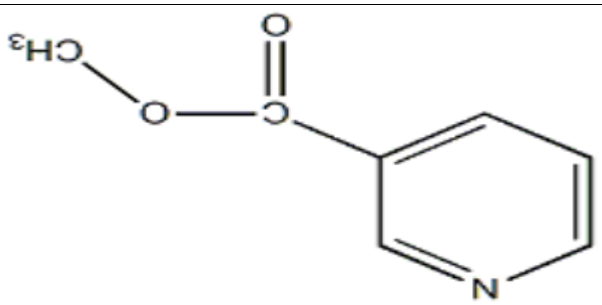
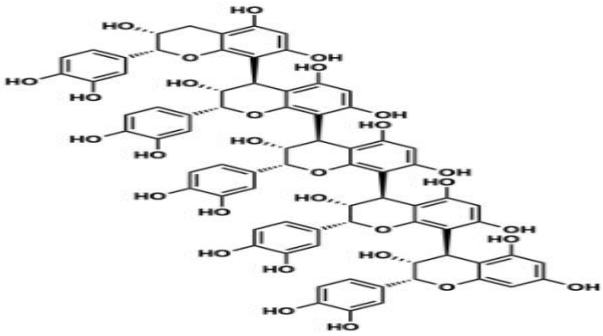
25	Methyl nicotinate	
26	Arecatannin A3	

Table 2. SMILES(Simplified Molecular Input Entry System) Pinang (*Areca catechu*)

Nu	Coumpound	SMILES
1.	4-HBA	O=C(O)c1ccc(O)cc1
2.	(+)-Catechin	Oc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)[C@@H](O)C2
3.	Lauric acid	CCCCCCCCCCCC(=O)O
4.	Myristic acid	CCCCCCCCCCCCCC(=O)O
5.	Myristoleic acid	CCCC/C=C/CCCCCCCC(=O)O
6.	Octadecanoic acid	CCCCCCCCCCCCCCCCCC(=O)O
7.	Arecaidine	CN1CCC=C(C(=O)O)C1
8	Arecoline	COC(=O)C1=CCCN(C)C1
9	Guvacine	O=C(O)C1=CCCNC1
10	Nicotine	CN1CCC[C@H]1c1cccnc1
11	Procyanidin B3	Oc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)[C@@H](O)[C@@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@@H](O)C2
12	Procyanidin B7	Oc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc2c(c1O)C[C@H](O)[C@@H](c1ccc(O)c(O)c1)O2
13	Procyanidin B1	Oc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@@H](O)C2
14	EEC	Oc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc2c(c1O)[C@H](c1c(O)cc(O)c3c1O[C@H](c1ccc(O)c(O)c1)[C@@H](O)C3)[C@@H](O)[C@@H](c1ccc(O)c(O)c1)O2
15	Arecatannin B1	Oc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc2c(c1O)C[C@H](O)[C@@H](c1ccc(O)c(O)c1)O2
16	Procyanidin C4	Oc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@@H](O)[C@@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@@H](O)C2
17	Arecatamnin A1	Oc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(

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Nu	Coumpound	SMILES
		O)c1)[C@@H](O)C2
18	EEEC	Oc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc2c(c1O)C[C@H](O)[C@@H](c1ccc(O)c(O)c1)O2
19	Arecatannin A2	Oc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@@H](O)C2
20	Proanthocyanidin A1	Oc1cc(O)c2c(c1)O[C@@]1(c3ccc(O)c(O)c3)Oc3cc(O)c4c(c3[C@@H]2[C@H]1O)O[C@H](c1ccc(O)c(O)c1)[C@@H](O)C4
21	Ethyl nicotinate	CCOC(=O)c1cccnc1
22	ENTPC	CCOC(=O)C1=CCCN(C)C1
23	ENPC	Cc1c(OCC(F)(F)F)ccnc1CS(=O)c1nc2ccccc2n1C(=O)N(C)CCOC(=O)C1CCN(C)CC1
24	Guvacoline	COC(=O)C1=CCCNC1
25	Methyl nicotinate	COC(=O)c1cccnc1
26	Arecatannin A3	Oc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@H](O)[C@H]2c1c(O)cc(O)c2c1O[C@H](c1ccc(O)c(O)c1)[C@H](O)C2

Table 3. Prediction of Antineoplastic and Apoptotic Activities of *Areca catechu* Compounds Using PASS Online

Nu	Compound	PA % Antifungi
1	4-HBA	0,384
2	(+)-Catechin	0,552
3	Lauric acid	0,407
4	Myristic acid	0,407
5	Myristoleic acid	0,498
6	Octadecanoic acid	0,407
7	Arecaidine	0,05
8	Arecoline	0,584
9	Guvacine	0,057
10	Nicotine	-
11	Procyanidin B3	0,534
12	Procyanidin B7	0,534
13	Procyanidin B1	0,534
14	EEC	0,584
15	Arecatannin B1	0,534
16	Procyanidin C4	0,534
17	Arecatannin A1	0,534
18	EEEC	0,584
19	Arecatannin A2	0,534
20	Proanthocyanidin A1	0,609
21	Ethyl nicotinate	0,257
22	ENTPC	-
23	ENPC	-

24	Guvacoline	0,116
25	Methyl nicotinate	0,258
26	Arecatannin A3	-

Table 4a. Analysis and Discussion of In Silico SwissADME Data Supporting the Antifungal Potential of *Areca catechu* Against Plant Pathogenic Fungi

Nu	compound	Water solubility		Lipophilicity (LogP)	Bioavailability score
		Log s (ESOL)	Class	Consensus Log $p_{o/w}$	
1	4-HBA	-2.07	Soluble	1.10	0.85
2	(+)-Catechin	-2.22	Soluble	0.70	0.55
3	Lauric acid	-3.07	soluble	3.71	0.85
4	Myristic acid	-3.98	Soluble	4.74	0.85
5	Myristoleic acid	-3.98	Soluble	4.46	0.85
6	Octadecanoic acid	-5.73	Moderately soluble	6.34	0.85
7	Arecaidine	0.77	Highly soluble	-0.44	0.55
8	Arecoline	-0.89	Very soluble	0.43	0.55
9	Guvacine	1.04	Highly soluble	-0.65	0.55
10	Nicotine	-1.89	Very soluble	1.34	0.55
11	Procyanidin B3	-5.14	Moderately soluble	1.40	0.17
12	Procyanidin B7	-5.14	Moderately soluble	1.40	0.17
13	Procyanidin B1	-5.14	Moderately soluble	1.40	0.17
14	EEC	-7.39	Poorly soluble	1.75	0.17
15	Arecatannin B1	-7.39	Poorly soluble	1.75	0.17
16	Procyanidin C4	-7.39	Poorly soluble	1.75	0.17
17	Arecatamnin A1	-7.39	Poorly soluble	1.75	0.17
18	EEEC	-	-	-	-
19	Arecatannin A2	-	-	-	-
20	Proanthocyanidin A1	-5.21	Moderately soluble	1.63	0.17
21	Ethyl nicotinate	-1.14	Very soluble	1.19	0.55
22	ENTPC	-1.14	Very soluble	0.79	0.55
23	ENPC	-4.95	Moderately soluble	2.69	0.55

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24	Guvacoline	-0.62	Very soluble	0.22	0.55
25	Methyl nicotinate	-1.53	Very soluble	0.80	0.55
26	Arecatannin A3	-	-	-	-

Table 4b. Analysis and Discussion of In Silico SwissADME Drug-Likeness Data Supporting the Antifungal Potential of *Areca catechu* Against Plant Pathogenic Fungi

Nu	Compound	Drug-likeness				
		Lipinski	ghose	veber	egen	muegge
1	4-HBA	Yes	No	Yes	Yes	No
2	(+)-Catechin	Yes	Yes	Yes	Yes	Yes
3	Lauric acid	Yes	Yes	Yes	Yes	Yes
4	Myristic acid	Yes	Yes	No	Yes	No
5	Myristoleic acid	Yes	Yes	No	Yes	No
6	Octadecanoic acid	Yes	No	No	No	No
7	Arecaidine	Yes	No	Yes	Yes	No
8	Arecoline	Yes	No	Yes	Yes	No
9	Guvacine	Yes	No	Yes	Yes	No
10	Nicotine	Yes	Yes	Yes	Yes	No
11	Procyanidin B3	No	No	No	No	No
12	Procyanidin B7	No	No	No	No	No
13	Procyanidin B1	No	No	No	No	No
14	EEC	No	No	No	No	No
15	Arecatannin B1	No	No	No	No	No
16	Procyanidin C4	No	No	No	No	No
17	Arecatamnin A1	No	No	No	No	No
18	EEEC	-	-	-	-	-
19	Arecatannin A2	-	-	-	-	-
20	Proanthocyanidin A1	No	No	No	No	No
21	Ethyl nicotinate	Yes	Yes	Yes	Yes	No
22	ENTPC	Yes	Yes	Yes	Yes	No
23	ENPC	Yes	No	No	Yes	No
24	Guvacoline	Yes	No	Yes	Yes	No
25	Methyl nicotinate	Yes	No	Yes	Yes	No
26	Arecatannin A3	-	-	-	-	-

Table 4c. In Silico Physicochemical Properties Data from SwissADME Supporting the Antifungal Activity of *Centella asiatica* to Eradicate Areca Catechu Fungi

Nu	Compound	Physicochemical								
		Molweight (gmol)	Num. heavy atoms	Num. Arom heavy Atoms	Fractioncsp3	Num. rotatebleb onds	Num. H-bond acceptors	Num. H-band donors	Molar refractivity	TPSA(A^{22})
1	4-HB[A]	138.12	10	6	0.00	1	3	2	35.42	57.53
2	(+)-Catechin	290.27	21	12	0.20	1	6	5	74.33	110.38

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Nu	Compound	Physicochemical								
		Molweight (gmol)	Num. heavy atoms	Num. Arom heavy Atoms	Fractioncsp3	Num. rotatablebonds	Num. H-bond acceptors	Num. H-band donors	Molar refractivity	TPSA(A^{22})
3	Lauric acid	200.32	14	0	0.92	10	2	1	61.57	37.30
4	Myristic acid	228.37	16	0	0.93	12	2	1	71.18	37.30
5	Myristoleic acid	226.36	16	0	0.79	11	2	1	70.71	37.30
6	Octadecanoic acid	284.48	20	0	0.94	16	2	1	90.41	37.30
7	Arecaidine	141.17	10	0	0.57	1	3	1	41.76	40.54
8	Arecoline	155.19	11	0	0.62	2	3	0	46.08	29.54
9	Guvacine	127.14	9	0	0.50	1	3	2	36.86	49.33
10	Nicotine	162.23	12	6	0.50	1	2	0	53.13	16.13
11	Procyanidin B3	578.52	42	24	0.20	3	12	10	146.71	220.76
12	Procyanidin B7	578.52	42	24	0.20	3	12	10	146.71	578.52
13	Procyanidin B1	578.52	42	24	0.20	3	12	10	146.71	578.52
14	EEC	866.77	63	36	0.20	5	18	15	219.09	331.14
15	Arecatannin B1	866.77	63	36	0.20	5	18	15	219.09	331.14
16	Procyanidin C4	866.77	63	36	0.20	5	18	15	219.09	331.14
17	Arecatamnin A1	866.77	63	36	0.20	5	18	15	219.09	331.14
18	EEEC	-	-	-	-	-	-	-	-	-
19	Arecatannin A2	-	-	-	-	-	-	-	-	-
20	Proanthocyanidin A1	576.50	42	24	0.20	2	12	9	144.14	209.76
21	Ethyl nicotinate	169.22	12	0	0.67	3	3	0	50.88	29.54
22	ENTPC	169.22	12	0	0.67	3	3	0	50.88	29.54
23	ENPC	595.63	41	15	0.48	13	11	0	149.68	126.07
24	Guvacoline	141.17	10	0	0.57	2	3	1	41.18	38.33
25	Methyl nicotinate	137.14	10	6	0.14	2	3	0	35.52	39.19
26	Arecatannin A3	-	-	-	-	-	-	-	-	-

Table 5. In Silico ADMET Data of *Areca catechu* Compounds Derived from pkCSM

Nu	Coumpound	Ames toxicity	Hepatotoxicity	Environmental toxicity	
				T.pyriformis toxicity (Log ug/L)	Minonow toxicity (Log mn)
1	4-HBA	No	No	-0.457	1.962
2	(+)-Catechin	No	No	0.395	2.306
3	Lauric acid	No	No	0.954	-0.084
4	Myristic acid	No	No	0.978	-0.601
5	Myristoleic acid	No	No	0.987	-0.474

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Nu	Coumpound	Ames toxicity	Hepatotoxicity	Environmental toxicity	
				T.pyriformis toxicity (Log ug/L)	Minonow toxicity (Log mn)
6	Octadecanoic acid	No	No	0.65	-1.565
7	Arecaidine	No	No	0.22	2.653
8	Arecoline	Yes	No	-0.508	2.488
9	Guvacine	No	No	-0.869	2.992
10	Nicotine	No	Yes	0.369	1.842
11	Procyanidin B3	No	No	0.285	5.13
12	Procyanidin B7	No	No	0.285	4.63
13	Procyanidin B1	No	No	0.285	5.13
14	EEC	No	No	0.285	12.011
15	Arecatannin B1	No	No	0.285	10.447
16	Procyanidin C4	No	No	0.285	11.773
17	Arecatamnin A1	No	No	0.285	11.773
18	EEEC	No	No	0.285	18.752
19	Arecatannin A2	No	No	0.285	20.177
20	Proanthocyanidin A1	No	No	0.285	4.123
21	Ethyl nicotinate	Yes	Yes	-0.425	2.323
22	ENTPC	Yes	Yes	-0.425	2.323
23	ENPC	No	Yes	0.285	0.702
24	Guvacoline	Yes	No	0.285	4.095
25	Methyl nicotinate	No	No	-0.193	1.839
26	Arecatannin A3	No	No	0.285	28.777

Based on Table 3, Areca catechu seeds contain various bioactive compounds with predicted antifungal activity, including phenolics, flavonoids, alkaloids, fatty acids, and proanthocyanidins. PASS Online analysis showed that Proanthocyanidin A1 exhibited the highest antifungal probability (Pa = 0.609), followed by arecoline, EEEC, and EEC (Pa = 0.584). These results indicate that polyphenolic compounds and alkaloids are the major contributors to the antifungal potential of betel nut seeds.

Phenolic compounds such as 4-hydroxybenzoic acid, (+)-catechin, and several procyanidins are known to inhibit fungal growth by disrupting cell membranes, inhibiting biofilm formation, and interfering with cell wall synthesis. Condensed tannins, including Procyanidin B1, B3, B7, and C4 (Pa = 0.534), also demonstrated promising antifungal activity against pathogenic fungi, including Candida albicans. Likewise, flavanol oligomers contribute through antioxidant mechanisms that suppress fungal survival. These findings agree with previous reports that the high flavonoid and tannin contents of A. catechu are responsible for its antimicrobial properties (Song *et al*., 2022; Wang *et al*., 2021).

Among alkaloids, arecoline showed the highest predicted antifungal activity (Pa = 0.584), whereas arecaidine, guvacine, and guvacoline displayed much lower Pa values. Alkaloids generally exert antimicrobial effects by disrupting membrane integrity and interfering with microbial metabolism (Sarma *et al*., 2026). Fatty acids such as lauric acid, myristic acid, myristoleic acid, and octadecanoic acid also contribute to antifungal activity by damaging fungal

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lipid membranes. Myristoleic acid showed the highest Pa value among fatty acids (0.498), although its predicted activity remained lower than that of proanthocyanidins and arecoline.

Some compounds, including nicotine, ENTPC, ENPC, and Arecatannin A3, showed no predicted antifungal activity in PASS Online, indicating limited contribution to the overall antifungal effect. Overall, the PASS analysis suggests that the antifungal activity of A. catechu results from synergistic interactions among phenolics, flavonoids, tannins, alkaloids, and fatty acids, with proanthocyanidins and arecoline representing the most active groups.

SwissADME analysis (Table 4a) revealed considerable variation in solubility, lipophilicity, and bioavailability among the compounds. Simple phenolics and alkaloids generally exhibited good aqueous solubility and moderate lipophilicity, favoring absorption and interaction with fungal targets. Fatty acids possessed higher LogP values, indicating stronger affinity for fungal lipid membranes, while compounds such as lauric acid also showed high bioavailability (0.85). In contrast, proanthocyanidins and condensed tannins exhibited lower bioavailability (0.17) due to their larger molecular size and greater polarity. However, they still demonstrated strong antifungal potential through surface interactions, protein precipitation, and inhibition of biofilm formation (Luiz *et al*., 2015).

SwissADME drug-likeness evaluation (Table 4b) identified (+)-catechin and lauric acid as the most promising compounds because they fulfilled all Lipinski, Ghose, Veber, Egan, and Muegge criteria. Their balanced physicochemical properties support efficient membrane transport and biological activity. Other compounds, including 4-hydroxybenzoic acid, arecoline, arecaidine, guvacine, guvacoline, and methyl nicotinate, satisfied most of the major drug-likeness rules, indicating acceptable absorption and permeability despite minor limitations.

Physicochemical analysis (Table 4c) further showed that catechin and alkaloids possess relatively low molecular weights and favorable polarity, supporting membrane permeability. Conversely, proanthocyanidins and condensed tannins have much larger molecular sizes, higher TPSA values, and numerous hydrogen-bonding groups, resulting in lower passive diffusion and bioavailability. Fatty acids exhibited high lipophilicity and low TPSA values, characteristics that facilitate interaction with fungal membranes and enhance antifungal action.

The pkCSM ADMET analysis (Table 5) indicated that some alkaloids, including arecoline, ethyl nicotinate, ENTPC, guvacoline, and nicotine, may present mutagenic or hepatotoxic risks. In contrast, (+)-catechin, 4-hydroxybenzoic acid, lauric acid, myristic acid, myristoleic acid, octadecanoic acid, arecaidine, guvacine, and Proanthocyanidin A1 were predicted to be non-mutagenic and non-hepatotoxic, indicating more favorable safety profiles. Although several proanthocyanidins showed relatively higher predicted aquatic toxicity, the overall ADMET evaluation suggests that (+)-catechin, lauric acid, myristic acid, myristoleic acid, and 4-hydroxybenzoic acid are the most promising antifungal candidates because they combine good predicted antifungal activity, favorable pharmacokinetic properties, and acceptable safety profiles. These compounds are therefore suitable for further validation through in vitro and in vivo studies.

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CONCLUSION

Areca catechu seeds contain various bioactive compounds, including phenolics, flavonoids, alkaloids, fatty acids, and proanthocyanidins, which exhibit potential antifungal activity. Their biological effects are mainly associated with membrane disruption, enzyme inhibition, and interference with fungal metabolic processes. The combination of these compounds suggests synergistic interactions that may enhance antifungal efficacy, supporting the potential development of effective and relatively safe natural biofungicides.

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