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Anticancer Activity of Phanera semibifida Extract Evaluated by Brine Shrimp Lethality Test (BSLT) and Molecular Docking Studies

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ORIGINAL ARTICLES

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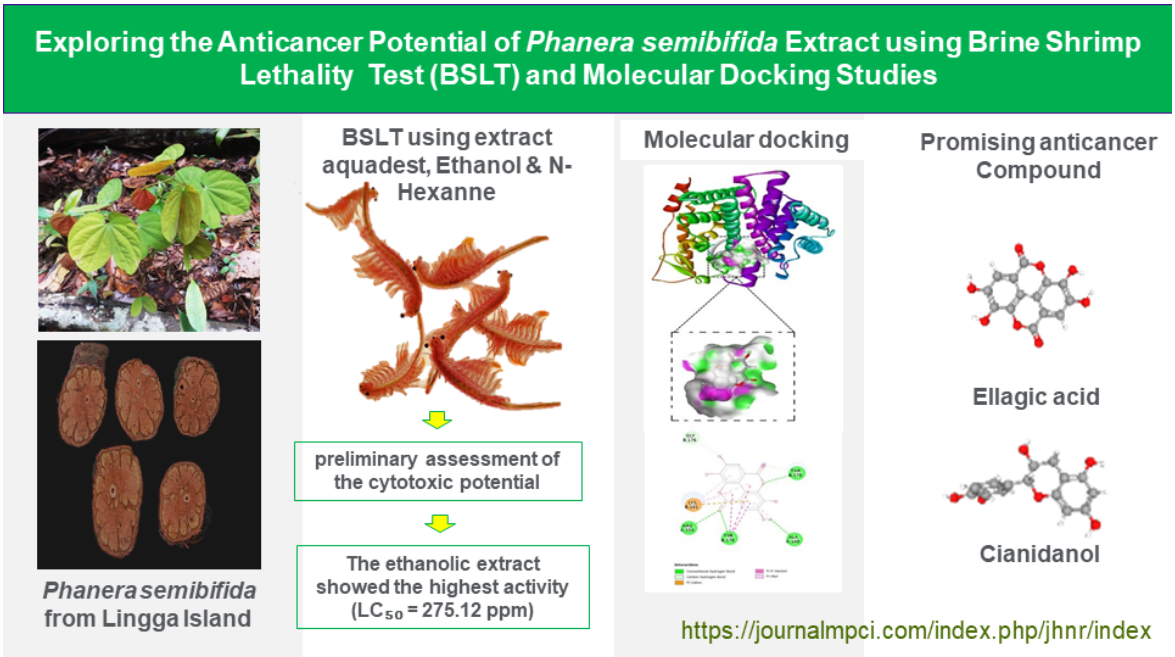
ABSTRACT

Indonesian people use plants as medicine because they are considered to have fewer side effects. The Lingga island community used Phanera semibifida (Roxb.) traditionally to make therapeutic drugs. P. semibifida has the potential to be a medicinal plant. We extracted stems and leaves with three different solvents and tested their cytotoxic activity. The ethanolic stem extract showed the highest value of LC_{50} in the moderate toxicity category. The ethanolic steam extract continued to be subjected to in silico analysis, using molecular docking. We selected four compounds for molecular docking studies against five cancer-related proteins. The proteins are Estrogen receptor α, CDK2, Human Cytochrome P450 CYP17A1, Cyclin A, and BCL-2. The result showed that Ellagic acid bound strongly to Estrogen receptor α, CDK2, CYP17A1, and Cyclin A protein. Cyanidanol showed the highest affinity to BCL-2. These results suggest that P. semibifida contains compounds that can target multiple cancer-related proteins. Our findings highlight its potential as a source of anticancer agents. We recommend isolating these compounds and testing their efficacy through in vitro and in vivo studies to confirm their therapeutic potential in future studies.

Key Messages:

- Phanera semibifida from Lingga Island exhibits cytotoxic activity in the Brine Shrimp Lethality Test.
- Four compounds in the ethanolic stem extract show potential in molecular docking as promising anticancer agents

GRAPHICAL ABSTRACT



INTRODUCTION

Indonesia is one of the most biodiverse countries, with thousands of plant species. Many of these plants have long been used in traditional medicine. Recent studies have provided scientific evidence of their pharmacological activities, including antimicrobial, antioxidant, antidiabetic, and anti-inflammatory effects. Several species also demonstrate potential in addressing degenerative disorders, including immunodeficiency, hepatitis, arthritis, stroke, osteoporosis, and cancer (1). Nevertheless, modern therapy relies heavily on single active compounds derived from pure isolates or synthetic drugs, which often yield limited therapeutic outcomes. The growing incidence of side effects linked to chemical drugs has further raised public concern. Consequently, researchers and communities have shown increasing interest in developing herbal-based remedies as safer and more sustainable alternatives (2).

Indonesian communities actively use plants in many aspects of their daily lives, particularly medicinal ones. They practice ethnomedicine by applying local plants, drawing on ancestral traditions and knowledge, to treat various illnesses (3). This traditional knowledge has been preserved and transmitted through successive generations (4). The Lingga community has a forest plant called *Phanera semibifida*, which is part of their traditional medicine (5). They include this plant in herbal formulations believed to maintain vitality and promote longevity (6). Previous studies have shown that *P. semibifida* provides antioxidant, anticancer, antidiabetic, anti-inflammatory, and other biological effects (7)

One commonly used approach to screen bioactive compounds in medicinal plants is the cytotoxicity assay using the brine shrimp lethality test (BSLT). This method employs *Artemia salina* larvae in vitro to determine the value of lethal concentration 50 (LC_{50}). An extract is considered toxic by the BSLT method if it exhibits an LC_{50} value below 1000 µg/mL (8). These methods also evaluate sample safety before application and help determine the biological activity of plant extracts (9). When BSLT results show promising activity, researchers advance the sample to more comprehensive investigations (10). Several studies report that BSLT results correlate with anticancer activity. These methods frequently use this simple, rapid, and reliable assay to discover new bioactive compounds, particularly potential anticancer agents from plants (11). However, despite its widespread application, the correlation between BSLT toxicity and specific anticancer mechanisms remains insufficiently explored. This limitation hinders the interpretation of cytotoxicity data in the context of molecular interactions. Consequently, integrating BSLT with molecular docking analysis could help elucidate the mechanistic basis of plant-derived compounds exhibiting cytotoxic effects. This computational technique enables high-throughput screening by pairing

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plant-derived compounds with cancer-related macromolecules and predicting the binding affinity of each ligand–receptor complex (11;12).

The docking study was specifically designed to predict the interactions between the major phytochemical constituents and selected cancer-associated proteins, thereby supporting the interpretation of BSLT results at the molecular level. Toxicity testing of *P. semibifida* originating from Lingga has not yet been reported, particularly regarding its anticancer potential. Therefore, this study aimed to evaluate the cytotoxic properties of *P. semibifida* extracts using the Brine Shrimp Lethality Test (BSLT) and to support their potential mechanisms of action through molecular docking analysis. Five cancer-associated proteins were selected as molecular targets, and the identified ligands from *P. semibifida* extracts were docked alongside commercial anticancer drugs as positive controls. The findings are expected to provide a scientific basis for future studies focused on isolating cytotoxic compounds and developing alternative anticancer agents derived from this plant, particularly those from the Lingga region.

METHODS

Preparation Toxicity Test

The samples used in the research are the stems and leaves of *Phanera semibifida* collected from Resun village, Lingga Islands, Riau Islands. The samples were prepared following Suhendra et al. 2025 methodology (14). This analysis was conducted at the Botany Laboratory of the Faculty of Mathematics and Natural Sciences, Riau University. The extraction was performed using three solvents: aquadest, ethanol PA, and N-hexane PA. Samples were extracted using the maceration method with a 1:10 ratio at room temperature, twice the maceration. After 24 hours, samples were filtered using Whatman filter paper No. 2. The samples were re-macerated in the new solution for 24 hours and filtered using the same filter paper. After that, the solution was evaporated using a rotary evaporator, resulting in a crude extract.

The toxicity test using the BSLT method begins with preparing brine shrimp larvae. The eggs of *Artemia salina* were obtained from an ornamental fish store in Pekanbaru. The eggs are hatched in a salt solution made from fish salt and aquadest with 30 ppm salinity and 8-9 pH. The larvae used in the toxicity test are 48 hours old. Subsequently, a sample solution is also prepared with several concentrations. Samples are dissolved using aquadest at concentrations of 1000, 100, and 10 ppm, with each concentration made in triplicate. After that, 10 larvae were placed in test tubes in every concentration and incubated for 24 hours. After the assay, the remaining Artemia larvae were used as feed for ornamental fish in the botany laboratory aquarium to minimize biological waste. The percentage of mortality larvae calculated using the formula:

$$\%\ larval\ death = \frac{total\ amount\ of\ dead\ larvae}{total\ amount\ of\ larva\ count} \times 100\%$$

Utilizing the anticancer potential from the best extracts.

Samples that produced the best results in the toxicity tests were further analyzed using molecular docking. We used coumpound from LCMS/MS results from previous research, which had anticancer activity. Lipinski's Rule of Five on the SwissADME web platform (http://www.swissadme.ch/) to prepare compounds before docking. We retrieved the 3D structures of the selected compounds from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and optimized their conformations using the Open Babel 2.3.1 plug-in integrated into PyRx 0.9 software. We used Estrogen receptor α (ID:2JF9), CDK 2 (ID: 2A4L), Human Cytochrome P450 CYP17A1 (ID:3RUK), BCL-2 (ID: 4LXD), and CyclinA (ID:6GUE), and ligand control (standard medicine)(15). We downloaded all macromolecules and their respective IDs from the RCSB PDB database (https://www.rcsb.org/). We prepared the proteins using the SwissModel web platform (https://swissmodel.expasy.org/), where we modeled the structures and removed water molecules and native ligands. Finally, we checked the receptor-bound ligands using Discovery Studio software and saved the processed structures in Protein Data Bank (.pdb) format.

Analysis Data

LC_{50} of BSLT were calculated using probit analysis in Microsoft Excel. The scatter chart is generated by entering the concentration log on the x-axis and the probit of larval mortality percentage on the y-axis.

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Linear trendline options, equation display, and R-squared value are added to the chart. The number 5 (the probability of 50% A. salina larval mortality) is substituted as y in the equation y = ax + b that appears on the graph. The value of log x, or the LC_{50} value of stem and leaf extracts against A. salina larvae, was sought. Based on Clarkson 2004, the determination of toxicity levels (LC_{50}) and their categories can be seen in Table 1.

Table 1. Category of the LC_{50} BSLT

LC 50 (ppm)	Categories
> 1000	Non-toxic
500-1000	Low toxicity
100-500	Moderately toxic
<100	Strongly toxic

Bioinformatic analysis which is molecular docking between macromolecules and ligands was carried out using AutoDock Vina in PyRx software. The grid box was adjusted to cover the entire protein surface, and the exhaustiveness value was set to 50 to improve sampling accuracy and minimize bias. The docking results were visualized and analyzed using PyMOL and Discovery Studio Visualizer 2016. The conformation with the lowest binding affinity and most stable interactions was selected to support the cytotoxicity results obtained from the BSLT assay.

RESULTS

The stem and leaves extract of *P. semibifida* exhibit differences. Based on previous research, the stem extract had phytochemical content more than the leaf sample (Suhendra et al., 2025). Toxicity testing with *A. salina* larvae also indicated differences under different conditions. The stem extract was generally more toxic than the leaf extract (Table 2). The LC_{50} value fell into the same category in Aquadest and N-Hexane solvents. That is low toxicity and non-toxic, respectively. However, the stem extract showed greater activity in ethanol than the leaf extract, indicating it is moderately toxic.

Table 2. Toxicity results and LC 50 of *P. semibifida* stem and leaves extract

Solvent	samples	Concentration (ppm)	Mortality ± SD	LC 50 (ppm)	Description
Aquadest	Leaves	1000	46.73 ± 1.24	922.57	Low toxicity
		100	43.33 ± 0.94		
		10	20.03 ± 0		
	Stems	1000	56.7 ± 0.47	659.39	Low toxicity
		100	30.0 ± 0.81		
		10	30 ± 0.81		
Ethanol	Leaves	1000	53.33 ± 0.47	789.80	Low toxicity
		100	33.33 ± 1.69		
		10	23.33 ± 1.24		
	Stems	1000	96.73 ± 0.47	275.12	Moderately toxic
		100	63.33 ± 1.24		
		10	16.73 ± 1.69		
N-hexane	Leaves	1000	33.33 ± 0.47	6660846	Non-toxic
		100	43.33 ± 0.94		
		10	26.73 ± 1.69		
	Stems	1000	40.0 ± 0.81	6478,8	Non-toxic
		100	43.3 ± 1.69		
		10	26.7 ± 1.69		

Based on these results, the ethanolic extract has the best value of LC50 compared to the other extracts. Therefore, this extract was selected for in silico analysis to evaluate its potential anticancer properties. LC-MS/MS analysis of the ethanolic stem extract was previously conducted by Suhendra et al. (2025). According to that study, the ethanolic stem extract contained 26 compounds, with seven compounds having potential as an anticancer. That is 13S-hydroxyoctadecadienoic acid (16), Ellagic acid

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(17), Cianidanol (18), Traumatic Acid (19), Catalposide (20), Quercetin-3'-glucuronide (21), and Apigetrin (22). Among these, four compounds complied with Lipinski's Rule of Five and continued to the molecular docking analysis. The compounds are 13S-hydroxyoctadecadienoic acid, ellagic acid, Cianidanol, and traumatic acid. The results of binding affinity and hydrogen bond interactions are presented in Table 3.

Table 3. Binding affinity results and hydrogen bond interactions

Protein	Ligand	Binding Affinity	H-Bond number	Residue (H-Bondlength, A)
Estrogen receptor α	13S-hydroxyoctadecadienoic acid	-4,1	1	ASP A:199 (2,701)
	Ellagic acid	-9,2	6	ARG A:153 (2,744); TYR B:178 (2,832); THR B:179 (2,136); ALA A:149 (2,49); THR B:179 (2, 564); GLY B:176 (2,288)
	Cianidanol	-6,8	5	HIS A: 232 (2,504); ASN B:174 (1,483); HIS B:96 (2.659); VAL B:177 (2,703) LYS B:191 (2,041)
	Traumatic Acid	-5,4	2	GLU B:72 (2,536); ARG B:113 (2,943)
	Tamoxifen	**-8,0**	**1**	**THR A:66 (3,075)**
CDK 2	13S-hydroxyoctadecadienoic acid	-5,9	2	ASP A:145 (3,018); LYS A:33 (3,113)
	Ellagic acid	-8,7	3	LEU A:83 (2,543); LYS A:33 (2,948); GLY A:11 (3,583)
	Cianidanol	-7,5	2	ASP A:86 (3014); GLY A:11 (3,578)
	Traumatic Acid	-5,8	2	LEU A:83 (2,237); LEU A:83 (3,114)
	Roscovitine	**-8,0**	**2**	**GLN A: 131 (2,431); LEU A: 83 (2,727)**
Human Cytochrome P450 CYP17A1	13S-hydroxyoctadecadienoic acid	-6,0	2	ALA A:87 (2,338); ASN A:184 (2,862)
	Ellagic acid	-8,0	2	ASP A:280 (2,191); ARG A:107 (2,910)
	Cianidanol	-7,3	3	ARG A:422 (2,304); ASP A:280 (2,295); ARG A:107 (3,204)
	Traumatic Acid	-4,8	0	
	Abiraterone	**-8,5**	**0**	
BCL-2	13S-hydroxyoctadecadienoic acid	-5,4	1	GLN A:77 (2,249)
	Ellagic acid	-6,6	7	ARG A:68 (2,402); SER A:64 (2,941); GLU A:111 (2,403); LYS A:22 (2,888); SER A:64 (3,067); ARG A:68 (3,235); SER A:75 (4,056)
	Cianidanol	-6,9	4	THR A:47 (2,621); GLU A:50 (2,749); ASN A:39 (2,792) SER A:49 (3,355)
	Traumatic Acid	-4,8	0	
	ABT99	**-6,5**	**4**	**ASN A:39 (2,481); ASN A:39 (3,169); ARG A:40 (3,082); GLU A:13 (3,372)**
CyclinA	13S-hydroxyoctadecadienoic acid	-5,3	1	ASN C:3 (2,234)
	Ellagic acid	-9,8	2	ILE C:10 (2,217); GLY C:13 (2,918)
	Cianidanol	-8,7	2	ASP C:86 (2,735)

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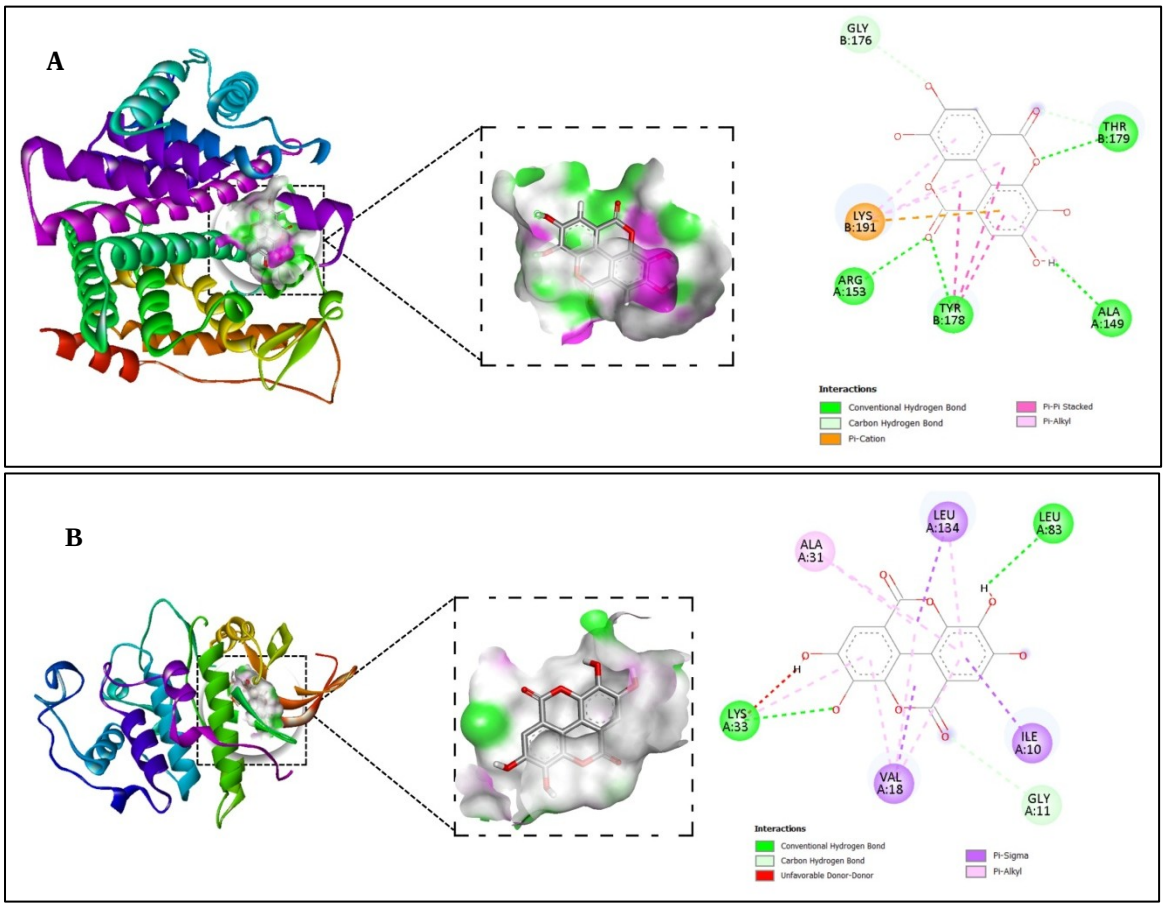
Protein	Ligand	Binding Affinity	H-Bond number	Residue (H-Bondlength, A)
	Traumatic Acid	-5,1	2	GLY C:13 (3,424) LEU C:267 (2,819); TYR C:269 (3,118)
	AZD5438	**-8,3**	**4**	**ILE A:10 (2,862); LYS A:129 (2,848); GLY A:13 (3,482); TYR A:15 (4,016)**

The interaction between Estrogen Receptor α and Ellagic Acid demonstrated the lowest binding affinity, with the highest number of hydrogen bonds and interacting residues, compared to all tested compounds, including the positive control (Tamoxifen). Similar results were observed for the interaction of ellagic acid with CDK2, human cytochrome P450 CYP17A1, and cyclin A. In this case, ellagic acid demonstrated a stronger binding affinity and greater hydrogen bond interactions than the respective positive controls (Roscovitine, Abiraterone, and AZD5438). Conversely, the BCL-2 protein demonstrated the strongest interaction with cyanidanol, demonstrating binding affinity, number of hydrogen bonds, and interacting residues comparable to the positive control ABT-99. These results indicate that ellagic acid and cyanidanol are the most promising anticancer candidates from *P. semibifida* stem extract.



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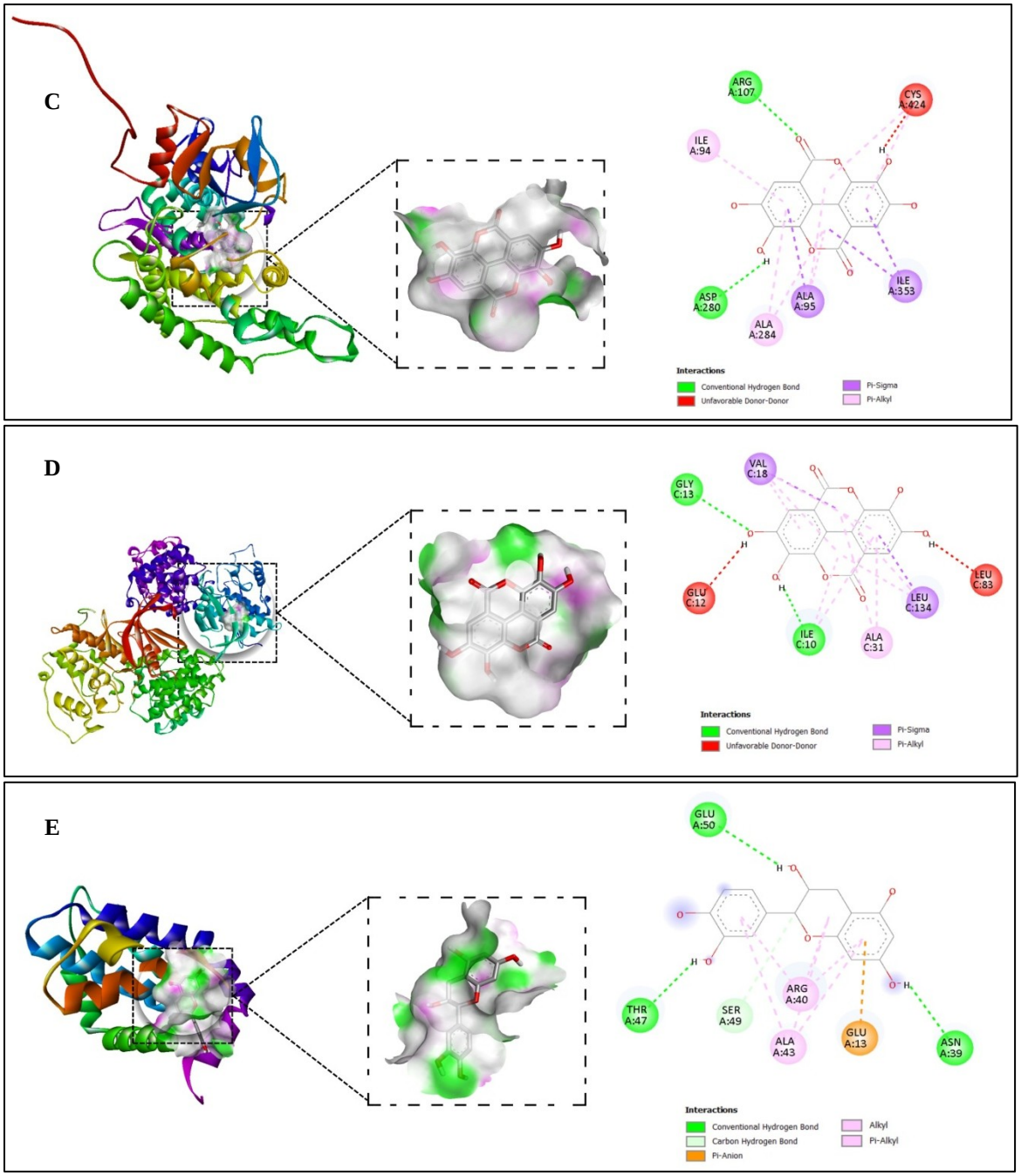

Figure 1. Interaction of A. ER α -Ellagic Acid, B. CDK 2- Ellagic Acid, C. Human Cytochrome P450 CYP17A1- Ellagic Acid, D. CyclinA- Ellagic Acid and E. BCL-2-Cianidanol.

The docking visualization illustrates the three-dimensional form of each target protein (left side), followed by the spatial fit of the ligand within its binding pocket (middle side), and the residues involved in the interaction (right side). The right side also points out several types of molecular contacts, including conventional hydrogen bonds (green), carbon–hydrogen bonds (yellow), and π-anion or π-alkyl interactions (orange and pink) (Figure 1). From the docking results, ellagic acid interacted closely with the active sites of Estrogen Receptor α, CDK2, Human Cytochrome P450 CYP17A1, and Cyclin A (Figure 2A–D). These interactions include several hydrogen and hydrophobic bonds with crucial residues, indicating a stable ligand–protein complex formation. Such stability supports the possible inhibitory role of this compound against proteins involved in cancer development. Likewise, the docking analysis of BCL-2 with cianidanol showed that the ligand binds strongly to the protein's active pocket, forming several hydrogen and hydrophobic interactions with residues. These contacts enhance the complex stability and suggest that

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cianidanol may effectively inhibit BCL-2 activity (Figure 2E).

DISCUSSION

Toxicity testing with *Artemia salina* larvae is a widely used pharmacological screening method because of its low cost, simplicity, and reliability, with a confidence level of up to 95% (15). The larvae possess a thin cuticle that increases their sensitivity to environmental changes and enables direct diffusion of test compounds into their bodies. Toxic samples induce larval mortality. Flavonoids can be toxic by reducing digestive enzyme activity and inhibiting nutrient absorption. These polyphenolic compounds are also known for their anticancer mechanisms and have promise as potential anticancer agents (23–25). Previous studies reported that *P. semibifida* from Lingga Island contains alkaloids, flavonoids, terpenoids, saponins, and tannins (14). Similarly, research on ethanol extracts of *P. semibifida* from West Sumatra showed that its LC_{50} value fell within the highly toxic category, indicating potential as an anticancer agent (26).

The results of the BSLT toxicity assay showed the lethal concentration 50 (LC_{50}), representing the extract concentration required to inhibit 50% of *A. salina* larvae. Lower LC_{50} values indicate higher levels of toxicity. The variation in LC_{50} values between the stem and leaf ethanolic extracts is likely related to differences in the number and the nature of compounds present. These differences can be attributed to the physicochemical properties of the compounds, which govern their solubility in ethanol. Ethanolic extract can. This interpretation is supported by the finding of Suhendra et al. (2025), who reported that LC-MS/MS analysis identified more compounds in the ethanol stem extract than the ethanol leaf extract. In addition, ethanol extracts are often used in anticancer research, one of which is *Begonia medicinalis* ethanol extract, which showed positive results in a colorectal cancer rat model (27). The plant part and extraction methods also influence the resulting bioavailability (28), and the choice of solvent further affects pharmacological activity (29).

In silico molecular docking provides complementary data to support the BSLT results. In this study, the ethanolic stem extract exhibited the highest toxicity as indicated by its LC_{50} value. Molecular docking of stem extract compounds with four cancer-related proteins, including targets associated with breast and prostate cancer, demonstrated strong interactions. These interactions highlight the potential of the compounds as anticancer agents. Low binding affinity values and many hydrogen bonds showed this potential. Ellagic acid showed the most activity on four target proteins: Estrogen receptor α, CDK2, Human Cytochrome P450 CYP17A1, and Cyclin A. Our compound had better binding affinities and more hydrogen bonds than the positive control compound (Table 3). Previous studies have reported that ellagic acid exhibits multiple biological activities, including antidiabetic, apoptosis-inducing, antioxidant, and anticancer effects (30). Cyanidanol exhibited the highest activity on the BCL-2 protein. This finding is consistent with previous studies on cyanidanol isolated from Ginkgo biloba, which demonstrated antioxidant and anticancer properties and showed positive effects against breast cancer (31).

These findings suggest that *P. semibifida* from Lingga possesses promising potential as an anticancer agent. Although BSLT is a widely used initial screening method, it cannot elucidate how active compounds inhibit cancer cell growth. Therefore, BSLT results should be complemented with in vitro assays, such as the MTT assay, to provide a more comprehensive evaluation. These data are essential for assessing the safety and therapeutic potential of *P. semibifida* for future development as a human medicinal preparation.

CONCLUSION

Phanera semibifida demonstrates anticancer potential based on toxicity test results. The ethanolic stem extract exhibited the highest activity and was classified as moderately toxic, with an LC_{50} value of 275.12 µg/mL, indicating its potential for development as an anticancer agent. In addition, ellagic acid and cyanidanol showed the strongest activity in the in-silico analysis. Future research should focus on isolating the active compounds from *P. semibifida* and evaluating their efficacy using in vitro and in vivo assays.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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