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Antioxidant and Anti-Breast Cancer Potentials of the Hydrophilic Fraction from Soft Coral *Nepthea sp.*: In Vitro and In Silico Assessment

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ABSTRACT. Soft corals of the genus *Nepthea* are recognized as rich sources of marine bioactive compounds, yet their hydrophilic metabolites remain poorly explored. This study characterized the hydrophilic fraction of *Nepthea sp.* and assessed its antioxidant and anti–breast cancer activities through *in vitro* and *in silico* approaches. Ethyl acetate extract (EAE) of *Nepthea sp.* was fractionated into six subfractions (F1–F6), with F5–F6 representing hydrophilic fractions. Phytochemical screening, TPC, TFC, and LC–MS/MS analyses were conducted alongside antioxidant (DPPH, ABTS), cytotoxicity (MTT, MCF-7), and molecular docking assays against xanthine oxidase (XO) and estrogen receptor alpha (ERα). Phytochemical profiling revealed alkaloids, phenolics, flavonoids, saponins, and terpenoids, with F5 exhibiting the highest TPC (73.11 mg GAE/g) and TFC (2.20 mg QE/g). LC–MS/MS identified rengyolester and piperolactam-C9:1(8E) in F5 and isosalsoline and 3-tert-butyl-4-methoxyphenol in F6. F5 demonstrated stronger antioxidant (DPPH IC_{50} = 67.39 mg/L; ABTS IC_{50} = 54.12 mg/L) and cytotoxic (MTT IC_{50} = 42.68 mg/L) activities than F6. Docking analysis supported these results: rengyolester and piperolactam-C9:1(8E) showed strong affinities toward XO (−8.4, −8.7 kcal/mol) and ERα (−7.6, −7.4 kcal/mol), forming interactions with key residues (Phe914, Phe1009, Glu353, Leu525) similar to reference ligands. The hydrophilic fraction particularly F5 contains multifunctional metabolites exhibiting both antioxidant and anticancer properties. The synergistic role of phenolic and terpenoid constituents highlights *Nepthea sp.* as a promising marine source of bioactive therapeutic leads.

Keywords: Antioxidant, breast cancer, hydrophilic fraction, molecular docking, *Nepthea sp.*

INTRODUCTION

Tropical oceans represent one of the richest biological resources, harboring a wide diversity of secondary metabolites with significant biological activities (Banday et al., 2024; Ibrahim et al., 2022). Marine organisms, including soft corals of the genus *Nepthea* sp., are known to produce various bioactive compounds such as diterpenoids, sesquiterpenes, and steroids, which exhibit broad pharmacological potential, including antioxidant, anti-inflammatory, and anticancer activities (Abdelhafez et al., 2021; Matulja et al., 2020). The exploration of marine-derived natural compounds has become increasingly relevant in the era of rising drug resistance and the urgent need for more selective alternative therapies target (Bandaru et al., 2025; Karthikeyan et al., 2022). Furthermore, the use of synthetic drugs and antioxidants from plants such as flavonoids can cause environmental damage through the formation of toxic phenolic compounds as a result of the degradation of these antioxidants (Osborn & Mahmud, 2019). Therefore, the search for new marine biota for these three activities is widely carried out.

Numerous studies have reported that extracts and fractions of *Nepthea* sp. exhibit high cytotoxic activity against several cancer cell lines, including MCF-7 (breast cancer) and A549 (lung cancer) cells (Abdelhafez et al., 2020; Sahidin et al., 2023). Non-polar and semi-polar fractions have generally been the primary focus, with findings indicating significant potential as anticancer and antioxidant agents. For instance, the ethyl acetate fraction of *Nepthea* sp. demonstrated strong antioxidant activity and cytotoxic effects against MCF-7 cells (Sadarun et al., 2022).

Despite extensive investigations on non-polar and semi-polar fractions, in-depth studies on polar or hydrophilic fractions of *Nepthea* sp. remain very limited. Hydrophilic fractions may contain phenolic compounds, flavonoids, and glycosides, which are well known for their strong antioxidant activity and

their ability to inhibit cancer cell proliferation through redox-related pathways (Hassan et al., 2023; Rafiudeen et al., 2024). This lack of data highlights an important scientific gap that warrants further exploration.

Breast cancer is one of the leading causes of cancer-related mortality among women worldwide. One of the key mechanisms underlying breast cancer development is excessive oxidative stress, which triggers genetic mutations and abnormal proliferation of mammary epithelial cells (Situmorang et al., 2026; Xiong et al., 2025). Therefore, natural compounds with strong antioxidant activity may serve both as preventive agents and as complementary therapies by targeting oxidative pathways involved in breast cancer progression (Griñan-Lison et al., 2021).

Based on the above considerations, this study aims to explore the molecular diversity of the hydrophilic fraction of *Nepthea* sp. and to evaluate its antioxidant and anticancer activities against breast cancer cells (MCF-7) using both in vitro and in silico approaches. The findings are expected to reveal potential compounds responsible for these biological activities and to expand the current knowledge of *Nepthea* sp. secondary metabolites as promising natural sources for the development of safer and more effective anticancer drugs.

EXPERIMENTAL SECTION

Materials

Samples of *Nepthea* sp. were collected from the Saponda waters, situated in Southeast Sulawesi Province, Indonesia. The collection was conducted by SCUBA diving at depths ranging from 4 to 10 meters. The taxonomic identification of the soft coral was carried out by qualified experts from the Faculty of Fisheries and Marine Science, Universitas Halu Oleo which is labelled 5871/UN29.12.1.1/PP/2023.

Extraction and Fractionation

Fresh specimens of *Nepthea* sp. weighing approximately 3 kg were first cleaned, cut into small segments, and subjected to maceration using ethyl acetate as the maceration solvent. The extraction process was performed three times, each with 10 liters of solvent, for a duration of 24 hours at ambient temperature to ensure optimal recovery of secondary metabolites. From 3 kg of wet material, yielded 160 g (5.3% w/w) of ethyl acetate extract (EAE). The extracts were concentrated by a vacuum rotary evaporator to get EAE. The 100 g EAE was fractionated by Vacuum Liquid Chromatography (VLC) with silica gel as the adsorbent. A solvent gradient system of n-hexane and ethyl acetate, starting from a nonpolar ratio (100:0) and gradually increasing to a polar ratio (0:100), was applied, followed by elution with 100% methanol.

Screening of Phytochemical Contents

Qualitative phytochemical screening of the hydrophilic fraction was performed to identify the presence of major secondary metabolites following standard procedures with slight modifications. Each extract that will be tested phytochemically is made at a concentration of 10,000 ppm including for alkaloids, flavonoids, terpenoids, phenolic and saponin (Fristiohady et al., 2024).

Total Phenolics and Total Flavonoids Content (TPC and TFC)

The total phenolic content (TPC) of the EAE was measured using the Folin–Ciocalteu reagent based on the method developed by Singleton and Rossi with slight modifications. Meanwhile, the total flavonoid content (TFC) was determined using the Chang method (Musdalipah et al., 2021).

LC-MS/MS Analysis

The compound profile of the sample was analyzed using LC-MS/MS following the standard operational procedure. Separation was carried out using a reverse-phase HSS T3 C18 column (2.1 × 100 mm, 1.8 µm particle size) maintained at 40 °C. The mobile phases consisted of solvent A (0.1% formic acid in water) and solvent B (acetonitrile containing 0.1% formic acid). Gradient elution was applied at a flow rate of 0.3 mL/min with an injection volume of 1 µL. The mass detection range was set from 50 to 1200 m/z. The source temperature was maintained at 120 °C, while the desolvation gas flow was set at 1000 L/h with a temperature of 500 °C. The capillary voltage and cone voltage were set at 2.0 kV and 30 V, respectively. The gradient program was as follows: 5% B (0–8 min), 40% B (8–11 min), and 100% B (11–16 min). Data-independent acquisition (MSE mode) was performed using low collision energy (6.00 eV) and high collision energy ranging from 10 to 40 eV. All LC-MS data were processed, including peak detection and analysis, using the UNIFI informatics platform (Sahidin et al., 2024).

Antioxidant Assays

The DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging activity was measured with slight modifications (Karmilah et al., 2024). The ABTS•+ (2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)) assay was performed following the method of with minor modifications (Yodha et al., 2023).

Cytotoxicity Potency In vitro

The cytotoxic activity of the samples was evaluated against human breast cancer (MCF-7) cell lines using the MTT colorimetric assay, which is based on the reduction of MTT into purple formazan crystals by metabolically active cells (Asasutjarit et al., 2021).

Molecular Docking Simulation

Because of their roles in oxidative stress and hormone-dependent breast cancer, respectively, xanthine oxidase (XO) and estrogen receptor alpha (ERα) were chosen as target proteins. The RCSB Protein Data Bank provided the crystal structures of XO (PDB ID: 3NRZ) and ERα (PDB ID: 3ERT) (Cao et al., 2010; Shiau et al., 1998) and made using MGLTools v1.5.6 (Arfan et al., 2024) by deleting ligands and water

molecules, adding polar hydrogens, and allocating Kollman charges. Ligand structures identified from fractions were retrieved from PubChem, optimized by adding hydrogen atoms, and assigned Gasteiger charges using the same software (Arfan et al., 2024).

AutoDock Vina 1.1.2 was used to run docking simulations using the default settings (Oleg & Arthur J., 2010). Docking validation was conducted by redocking hypoxanthine into XO and 4-hydroxytamoxifen into ERα, with RMSD values < 2 Å (**Table 1**) (Arfan et al., 2025). Docking was carried out at the binding sites of the native ligands using grid sizes of 20 × 20 × 20 Å for XO and 30 × 30 × 30 Å for ERα. Binding affinities and interactions were analyzed using Discovery Studio Visualizer.

RESULT AND DISCUSSION

Extraction and Fractionation

The extraction of *Nepthea sp.* yielded 160 g (5.3% w/w), indicating that the extraction process using ethyl acetate was efficient and well-performed. This result is consistent with previous studies reporting that ethyl acetate extraction of soft coral samples typically produces yields in the range of 3–6% (Kasimala et al., 2026; Peng et al., 2018; Imran et al., 2025). This fractionation process resulted in six fractions (F1–F6) with yields: F1 = 35.2 g, F2 = 4.3 g, F3 = 5.9 g, F4 = 10.7 g, F5 = 26.5 g, and F6 = 15.4 g. Polarity and TLC analysis classified F1–F2 as hydrophobic, F3–F4 as semi-hydrophilic, and F5–F6 as hydrophilic fractions.

The fraction F1 yielded the highest yield (35.2 g), followed by fraction F5 (26.5 g) and fraction F6 (15.4 g). The dominance of F1 suggests a high presence of terpenoids such as cembranes and briaranes, known for cytotoxic properties (Abdelhafez et al., 2021; Matulja et al., 2020). Meanwhile, the substantial yield of hydrophilic fractions (**F5–F6**, total 41.9 g) implies notable production of polar secondary metabolites like phenolic acids, flavonoid glycosides, and polar terpenoids. This fractionation profile demonstrates the metabolic diversity of *Nepthea sp.*, reflecting its adaptive biosynthesis to marine stressors such as UV exposure and microbial competition. Hydrophobic metabolites typically exhibit cytotoxic activity, whereas hydrophilic ones contribute to antioxidant defense (Park et al., 2015).

Phytochemical Screening, Total Phenolic and Flavonoid Content (TPC and TFC)

Phytochemical screening of the hydrophilic fractions (**F5–F6**) of *Nepthea sp.* revealed the presence of several classes of secondary metabolites including alkaloids, flavonoids, phenolics/tannins, saponins, and terpenoids (**Table 1**). Both fractions exhibited a similar qualitative composition, but differed in intensity. Fraction **F5** demonstrated higher abundance in phenolic and terpenoid constituents, while **F6** showed relatively lower but still significant levels of the same metabolites.

The strong detection of phenolics and terpenoids in both hydrophilic fractions indicates that *Nepthea sp.* synthesizes a complex array of bioactive metabolites belonging to multiple biosynthetic pathways. The coexistence of terpenoid and phenolic compounds is consistent with the unique chemical diversity observed in marine soft corals, which produce mixed metabolic profiles combining polyketide- and isoprenoid-derived metabolites. Phenolic compounds play crucial roles as hydrogen or electron donors in antioxidant reactions, whereas terpenoids contribute to cytotoxic and anti-proliferative activities through modulation of apoptosis-related signaling pathways. The simultaneous occurrence of both compound types suggests that these hydrophilic fractions may exhibit dual antioxidant and anticancer potential, aligning with the objectives of this study. Quantitative estimation of total phenolic content (TPC) and total flavonoid content (TFC) was further performed using spectrophotometric methods based on the Folin–Ciocalteu and aluminum chloride colorimetric assays, respectively. The results are summarized in **Table 2**.

Table 1. Phytochemical screening results of hydrophilic fractions of *Nepthea sp*.

Fraction	Weight (g)	Alkaloids	Flavonoids	Phenolics	Saponins	Terpenoids
F5	26.5	++	+	+++	+	+++
F6	15.4	++	+	++	+	++

Note: (+) = presence (low), (++) = moderate, (+++) = strong intensity.

Table 2. Total phenolic (TPC) and total flavonoid (TFC) contents of hydrophilic fractions of *Nepthea sp.*

Method	Hydrophilic Fractions	
	F5	F6
TPC (mg GAE/g extract)	73.11 ± 1.33	68.77 ± 0.98
TFC (mg QE/g extract)	2.20 ± 0.21	2.22 ± 0.25

The results demonstrated that the total phenolic content in the hydrophilic fractions was relatively high, with **F5** (73.11 ± 1.33 mg GAE/g) slightly exceeding **F6** (68.77 ± 0.98 mg GAE/g). This indicates that fraction **F5** contains a richer pool of phenolic constituents, which correlates with the qualitative screening showing strong (+++) phenolic intensity. Conversely, the total flavonoid contents were relatively low and statistically similar in both fractions (around 2.2 mg QE/g extract), suggesting that flavonoids represent only a minor phenolic subclass within these extracts. High TPC values in both fractions are consistent with other marine-derived extracts exhibiting antioxidant potential, as soft corals such as *Sinularia* sp. and *Lobophytum* sp. (Sahidin et al., 2022; Xie et al., 2025).The slightly higher phenolic yield in **F5** may be attributed to more polar phenolic acids or hydroxylated diterpenoids that preferentially elute in the early hydrophilic fraction. The relatively low TFC compared to TPC indicates that non-flavonoid phenolic compounds, such as simple phenolic acids or phenolic terpenoids, are the dominant antioxidant constituents in these hydrophilic fractions.

This observation agrees with reports that *Nepthea* species predominantly produce phenolic diterpenes and sesquiterpenoids, rather than typical flavonoids found in terrestrial plants (Amir et al., 2012). These findings confirm that the hydrophilic fractions of *Nepthea sp.* are chemically enriched in phenolic and terpenoid metabolites, providing a strong biochemical basis for their antioxidant and anticancer activities. The significant phenolic concentration, particularly in **F5**, supports the hypothesis that polar components contribute markedly to the observed bioactivity. These results warrant further investigation through LC–MS/MS-based molecular profiling and in vitro/in silico bioassays to identify specific compounds responsible for the biological effects.

LC–MS/MS Profiling and Compound Identification

LC–MS/MS analysis of fraction **F5** resulted in six major compounds with observed *m/z* values between 118.0858 and 800.6053. The most abundant ions were detected at *m/z* 295.1544 and 352.1909, corresponding respectively to Rengyolester and Piperolactam-C9:1(8E) (**Table 3**).

Fragmentation analysis (**Figure 1A–C**) indicated that *m/z* 295.1544 (Rengyolester) produced daughter ions at *m/z* 217.1223 and 184.0736, consistent with ester bond cleavage and rearrangement of the phenolic moiety (Sadarun et al., 2025). Similarly, *m/z* 352.1909 (Piperolactam-C9:1) exhibited major fragments at *m/z* 241.1216 and 137.0593, confirming the presence of an amide–lactone structure typical of piperolactam analogs found in marine-derived fungi and corals (Sahidin et al., 2024).

The presence of Rengyolester and Piperolactam-C9:1(8E) is significant because these metabolites are associated with antioxidant and cytotoxic properties. Rengyolester, a phenolic ester bearing a phenolic unit, an ester group, and two hydroxyl groups, has been associated with strong antioxidant activity, likely through hydrogen atom donation via its hydroxyl moieties, consistent with the radical-scavenging mechanism reported for phenolic esters (Arzola-Rodríguez et al., 2022). Meanwhile, piperolactam derivatives, have demonstrated cytotoxic effects against cancer cell lines, including MCF-7 breast cancer cells, through apoptosis induction and modulation of oxidative stress-related signaling pathways (Chen et al., 2019). Furthermore, the detection of high-mass ions (*m/z* 562.37 and 800.60), suggests the presence of nitrogen-containing terpenoid derivatives, consistent with the nitrogenous secondary metabolite profile previously reported in *Nepthea* sp. from Southeast Sulawesi (Sahidin et al., 2023). The incorporation of nitrogen into a high-carbon terpenoid backbone is characteristic of terpenoid–alkaloid conjugates, a class known for diverse bioactivities including antioxidant and cytotoxic properties (Wang et al., 2024).

Fraction F6 exhibited seven dominant peaks with observed m/z values ranging from 118.0858 to 544.3397. The lower-mass peaks (m/z 118.0858, 181.1218, and 194.1172) correspond to Valine, 3-tert-butyl-4-methoxyphenol, and Isosalsoline, respectively (**Table 4**).

Table 3. LC–MS/MS compound identification in fraction **F5** of *Nepthea sp*.

No	Rt (min)	Observed [M+H]/ [M+Na] (m/z)	Experimental Neutral Mass (Da)	Theoretical Monoisotopic Mass (Da)	Mass error (mDa)	Compound Name	Reference
1	1.86	118.0858	117.07898	117.078979	-0.4	Valine	(Sahidin et al., 2023)
2	2.05	158.1172	157.11028	157.110279	-0.3	Candidate $C_8H_{15}NO_2$	-
3	9.94	562.3747	561.36655	561.366552	0.8	Candidate $C_{32}H_{51}NO_7$	-
4	10.15	800.6053	777.61723	777.617229	-1.2	Candidate $C_{52}H_{79}N_3O_2$	-
5	10.23	295.1544	294.14672	294.146724	0.4	Rengyolester	(Sadarun et al., 2025)
6	10.31	352.1909	329.19909	329.199094	2.5	Piperolactam-C9:1(8E)	(Sahidin et al., 2024)

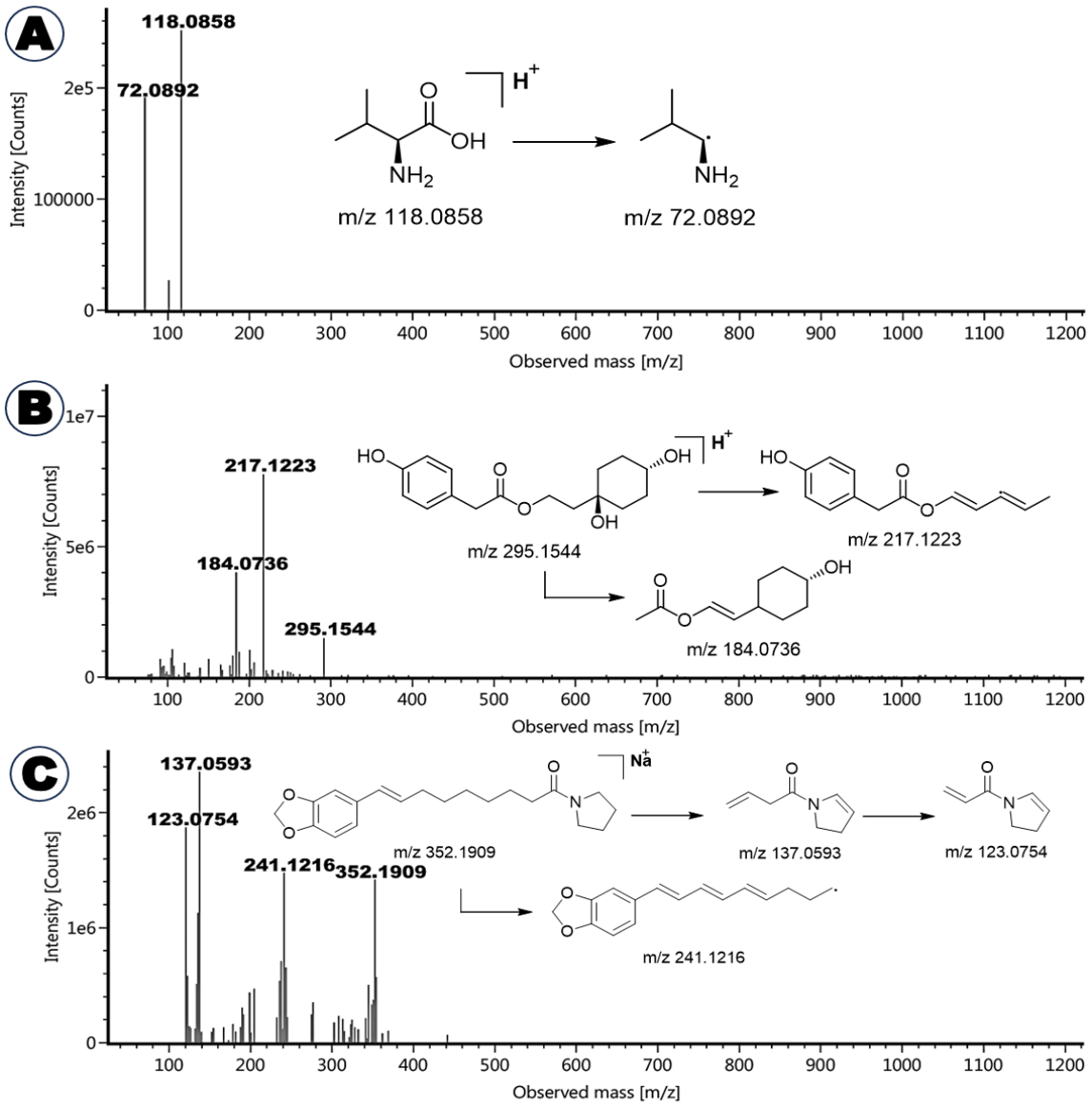

Figure 1. Electrospray ionization (ESI) MS^n fragmentation profiles of the characterized compounds present in fraction F5; (**A**) Valine, (**B**) Rengyolester, (**C**) Piperolactam-C9:1(8E)

Table 4. LC–MS/MS compound identification in fraction **F6** of *Nepthea sp.*

No	Rt (min)	Observed [M+H]/ [M+Na] (m/z)	Experimental Neutral Mass (Da)	Theoretical Monoisotopic Mass (Da)	Mass error (mDa)	Compound Name	Reference
1	1.85	118.0858	117.0789	117.078979	-0.5	Valine	(Sahidin et al., 2023)
2	2.06	194.1172	193.1103	193.110279	-0.3	Isosalsoline	(Imran et al., 2025)
3	6.62	181.1218	180.1150	180.115030	-0.5	3-tert-Butyl-4-methoxyphenol	(Fusvita et al., 2025)
4	8.25	185.1143	162.1256	162.125594	-0.5	Candidate $C_8H_{18}O_3$	-
5	8.35	266.1748	265.1678	265.167794	-0.3	Candidate $C_{15}H_{23}NO_3$	-
6	10.10	544.3397	521.3505	521.350509	0.0	Candidate $C_{33}H_{47}NO_4$	-
7	14.86	482.3607	459.3712	459.371244	0.3	Candidate $C_{29}H_{49}NO_3$	-

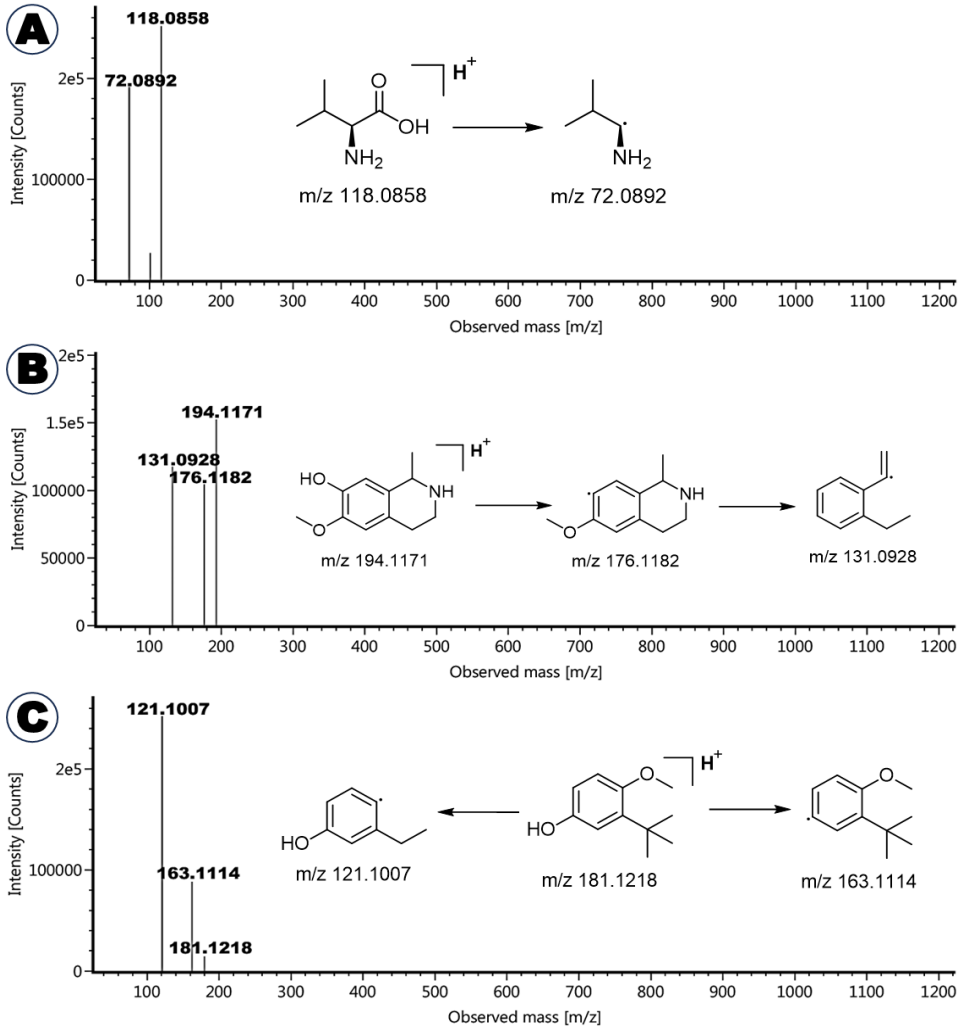

Figure 2. Electrospray ionization (ESI) MS^n fragmentation profiles of the characterized compounds present in fraction F6; (**A**) Valine, (**B**) Isosalsoline, (**C**) 3-Tert-butyl-4-methoxyphenol

The fragmentation pattern (**Figure 2A–C**) confirmed these assignments *m/z* 194.1171 (Isosalsoline) produced daughter ions at *m/z* 176.1182 and 131.0928, typical of β-carboline fragmentation (Imran et al., 2025). In *m/z* 181.1218 (3-tert-butyl-4-methoxyphenol) yielded fragments at *m/z* 163.1114 and 121.1007, indicative of demethylation and loss of alkyl groups from the phenolic ring (Fusvita et al., 2025). Isosalsoline has been reported to exert neuroprotective and radical-scavenging effects (Shang et al., 2020), while 3-tert-butyl-4-methoxyphenol acts as a lipid peroxidation inhibitor due to its phenolic hydroxyl group (Hoang & Park, 2024). Interestingly, **F6** also contained medium-to high-mass ions (*m/z* 482.36 and 544.33), which are consistent with nitrogen-bearing terpenoid derivatives, possibly sesqui- or diterpenoid alkaloids. Such terpenoid metabolites from *Nephthea* sp. have been reported to exhibit considerable binding affinities toward target proteins including EGFR, HER2, and VEGF, suggesting their potential role as tyrosine kinase inhibitory molecules that may underlie the observed anticancer properties of this fraction (Abdelhafez et al., 2021).

Comparatively, both **F5** and **F6** shared the amino acid Valine (m/z 118.0858), indicating a possible role in peptide-based metabolites. **F5** was richer in complex esterified terpenoids (Rengyolester and Piperolactam-C9:1), whereas **F6** was dominated by small phenolic and alkaloidal molecules such as Isosalsoline and 3-tert-butyl-4-methoxyphenol. This compositional difference suggests that **F5** may primarily contribute to cytotoxic and anti-breast cancer activity, while **F6** exhibits stronger antioxidant potential. The integration of LC–MS/MS data with the phytochemical and TPC/TFC findings confirms that the hydrophilic fractions of *Nepthea sp.* harbor both small-molecule antioxidants and complex terpenoid-amide compounds. These molecules collectively underlie the dual antioxidant–anticancer bioactivity observed in this species, providing new molecular insights into its pharmacological relevance.

In Vitro Antioxidant and Cytotoxic Activities

The antioxidant and cytotoxic activities of the hydrophilic fractions (**F5** and **F6**) of *Nepthea sp.* were evaluated using the DPPH and ABTS radical scavenging assays and the MTT cell viability assay, respectively. The antioxidant activity against DPPH and

ABTS radicals, reflected by the ability to reduce radical compounds, is presented in **Table 5**. The DPPH assay is based on the ability of antioxidant compounds to donate hydrogen atoms, whereas the ABTS assay evaluates the ability of compounds to stabilize free radicals through proton donation (Yodha et al., 2023). The results indicate that the radical scavenging capacity against ABTS is higher than that of DPPH. This is because ABTS reacts more rapidly with antioxidants, is soluble in both aqueous and organic solvents, can be applied across a wider pH range, and exhibits higher sensitivity compared to the DPPH method, which is generally limited to acidic conditions (Ilyasov et al., 2020).

Radical reduction capacity is expressed as the IC_{50} value. In general, antioxidant activity based on IC_{50} values is classified as follows: >200 μg/mL indicates no activity, 150–200 μg/mL weak, 100–150 μg/mL moderate, 50–100 μg/mL strong, and <50 μg/mL very strong (Hamsidi et al., 2024).

Both hydrophilic fractions demonstrated radical scavenging capacity, with **F5** showing markedly stronger antioxidant activity compared to **F6**. The IC_{50} values of **F5** were 67.39 ± 1.71 mg/L (DPPH) and 54.12 ± 1.18 mg/L (ABTS), while F6 displayed higher IC_{50} values (moderate activity) at 101.10 ± 2.11 mg/L and 89.76 ± 1.44 mg/L, respectively.

The superior performance of **F5** can be attributed to its higher total phenolic content (73.11 mg GAE/g extract) compared to **F6** (68.77 mg GAE/g extract), as phenolic compounds are well-established hydrogen or electron donors that neutralize free radicals. Mechanistically, the antioxidant action of these fractions can be linked to the molecular presence of rengyolester (m/z 295.1544) and 3-tert-butyl-4-methoxyphenol (m/z 181.1218), identified in the LC–MS/MS analysis. Both molecules possess phenolic hydroxyl groups capable of hydrogen donation and resonance stabilization of free radicals. The slightly higher activity observed in the ABTS assay compared to DPPH suggests that the phenolic compounds in **F5** are more efficient in scavenging hydrophilic radicals, consistent with their polarity. These results indicate that the hydrophilic fractions, particularly **F5**, act as effective free-radical scavengers, supporting their potential as antioxidant agents from marine-derived sources.

The cytotoxic effects on MCF-7 cancer cells, as determined by the MTT assay, are presented in **Table 6**. Intracellular reduction of MTT is mediated by oxidoreductase and dehydrogenase enzymes, along with electron donors at various stages of the glycolytic pathway through to the mitochondrial electron transport chain, enabling the measurement of cell proliferation and viability (Ghasemi et al., 2023). Cytotoxic activity is classified based on IC_{50} values (the concentration that inhibits 50% of cell growth) according to the National Cancer Institute (NCI) as follows: active/potent at ≤ 30 mg/L, moderate at 30–100 mg/L, and weak at > 100 mg/L (Trujillo et al., 2023).

The cytotoxic potential of fractions **F5** and **F6** was assessed against breast cancer cells using the MTT assay. The results revealed significant differences between the two fractions: **F5** moderate cytotoxic activity with an IC_{50} of 42.68 ± 0.86 mg/L, whereas **F6** showed weaker cytotoxicity with an IC_{50} of 108.34 ± 1.85 mg/L.

The pronounced cytotoxicity of **F5** suggests a higher concentration of bioactive terpenoid and amide compounds, consistent with the LC–MS/MS identification of piperolactam-C9:1(8E) and rengyolester in this fraction. Piperolactam derivatives are known to induce mitochondria-mediated apoptosis and cell cycle arrest in various cancer cell lines, while phenolic esters like rengyolester may exert cytoprotective or pro-apoptotic effects depending on concentration.

In contrast, the weaker cytotoxicity of **F6** aligns with its chemical composition dominated by small phenolic antioxidants such as 3-tert-butyl-4-methoxyphenol and isosalsoline, which are more likely to act as radical scavengers than as cytotoxic agents. Thus, the differential biological responses between **F5** and **F6** emphasize a bioactivity dichotomy. **F5** cytotoxic and antioxidant dual activity (dominated by terpenoid-phenolic compounds) and **F6** predominantly antioxidant (dominated by small phenolic and alkaloidal molecules). Comparative interpretation indicates that the cytotoxic potency of **F5** (IC_{50} 42.68 mg/L) is within the range considered moderately active for natural product fractions (IC_{50} < 50 mg/L), supporting its potential role as a lead extract for anticancer compound isolation.

Table 5. Antioxidant activity of hydrophilic fractions of *Nepthea sp.*

Method	Hydrophilic Fractions (IC_{50}, mg/L)		
	F5	**F6**	Ascorbic Acid
DPPH	67.39 ± 1.71	101.10 ± 2.11	8.30 ± 0.23
ABTS	54.12 ± 1.18	89.76 ± 1.44	8.84 ± 0.26

Table 6. Cytotoxic activity of hydrophilic fractions of *Nepthea sp.*

Method	Hydrophilic Fractions (IC_{50}, mg/L)		
	F5	**F6**	Doxorubicin
MTT	42.68 ± 0.86	108.34 ± 1.85	4.91 ± 0.48

A clear correlation was observed between the phenolic richness (TPC), radical scavenging capacity (DPPH/ABTS), and cytotoxic effect (MTT) of the fractions. **F5** consistently showed superior performance across all assays, suggesting that phenolic–terpenoid synergy contributes to both antioxidant and anticancer activities.

The in vitro results strongly support that the hydrophilic fraction (**F5**) of *Nepthea sp.* exhibits potent antioxidant and cytotoxic properties, attributed to its phenolic–terpenoid content and molecular diversity. This establishes **F5** as a promising candidate for further *in silico* evaluation targeting breast cancer therapy.

In Silico Molecular Docking and Interaction Analysis

Molecular docking was performed to support and rationalize the *in vitro* antioxidant and cytotoxic results obtained for the hydrophilic fractions (**F5** and **F6**) of *Nepthea sp.* Two target proteins were selected to represent the biological endpoints: xanthine oxidase (XO) for antioxidant activity and estrogen receptor alpha (ERα) for anti–breast cancer potential.

The molecular docking investigation of the compounds identified in **F5** and **F6** against xanthine oxidase provided mechanistic insights that supported the observed *in vitro* antioxidant activities. The binding energies revealed that piperolactam-C9:1(8E) (−8.7 kcal/mol) and rengyolester (−8.4 kcal/mol) exhibited stronger binding affinities than the reference ligand hypoxanthine (HPA, −6.5 kcal/mol), while ascorbic acid, used as the control, displayed a lower binding energy of -6.0 kcal/mol. In contrast, smaller molecules such as isosalsoline, 3-tert-butyl-4-methoxyphenol, and valine showed relatively weaker affinities (−5.9 to −4.9 kcal/mol).

Figure 3 illustrates the docking poses and key interactions of the compounds with the XO active site. Interaction analysis demonstrated that aromatic residues Phe914 and Phe1009 contributed significantly to hydrophobic stabilization in all ligands, including HPA. Hydrogen bonding with Thr1010 and Val1011 was observed for rengyolester, valine, and HPA, whereas Glu802 mediated electrostatic stabilization in complexes involving HPA, valine, and isosalsoline. In contrast, ascorbic acid, used as the control, exhibited multiple hydrogen bond interactions with Glu802, Arg880, Thr1010, Val1011, and Ala1079, without any observable hydrophobic contacts. This interaction profile indicates that its binding is predominantly governed by polar interactions, which may contribute to its comparatively lower binding affinity to the other ligands. The relatively weak affinity of 3-tert-butyl-4-methoxyphenol corresponded to its exclusive hydrophobic interaction profile, consistent with its small, phenolic structure and limited polar moieties. **Table 7** summarizes the docking energies and specific molecular interactions.

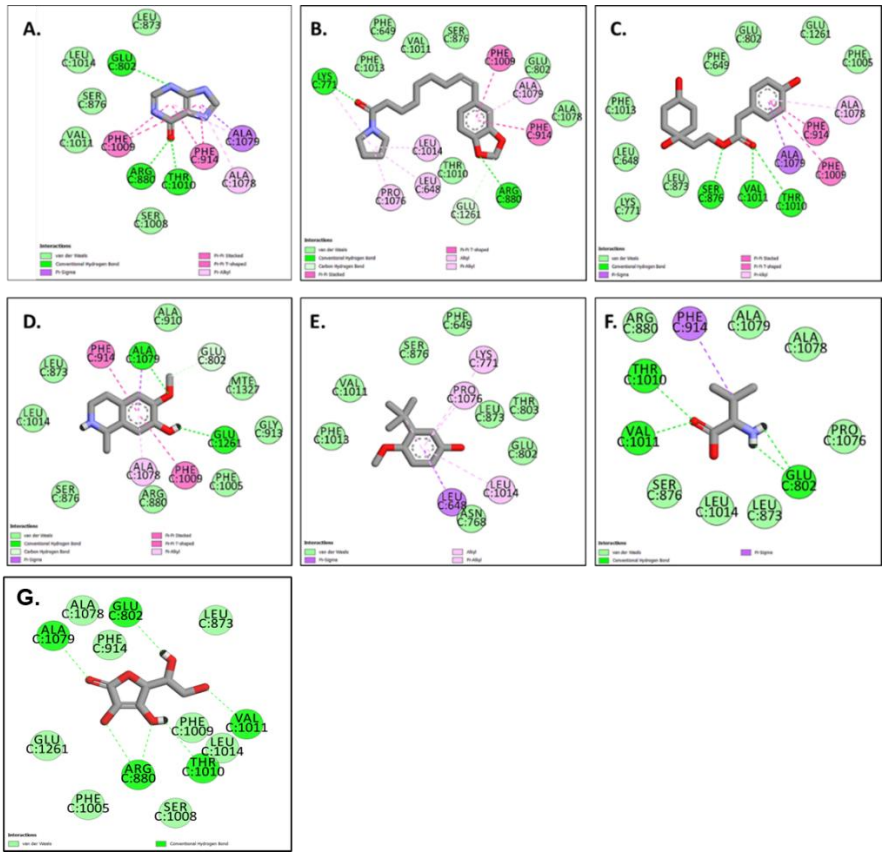

Figure 3. Molecular interactions of (A) HPA, (B) piperolactam-C9:1(8E), (C) rengyolester, (D) isosalsoline, (E) 3-tert-butyl-4-methoxyphenol, (F) valine and (G) ascorbic acid with xanthine oxidase.

Table 7. Molecular interactions of compounds from the hydrophilic fraction (EAE) of *Nepthea* sp. against xanthine oxidase.

Compounds	Binding energy (kcal/mol)	H-bond interaction	Hydrophobic interaction
Piperolactam-C9:1(8E)	−8.7	Lys771, Arg880, Glu1261	Leu648, Phe914, Phe1009, Leu1014, Pro1076, Ala1079
Rengyolester	−8.4	Ser876, Thr1010, Val1011	Phe914, Phe1009, Ala1078, Ala1079
Hypoxanthine (HPA)	−6.5	Glu802, Arg880, Thr1010	Phe914, Phe1009, Ala1078, Ala1079
Ascorbic Acid	-6.0	Glu802, Arg880, Thr1010, Val1011, Ala1079	-
Isosalsoline	−5.9	Glu802, Ala1079, Glu1261	Phe914, Phe1009, Ala1078
3-tert-butyl-4-methoxyphenol	−5.3	–	Leu648, Lys771, Leu1014, Pro1076
Valine	−4.9	Glu802, Thr1010, Val1011	Phe914

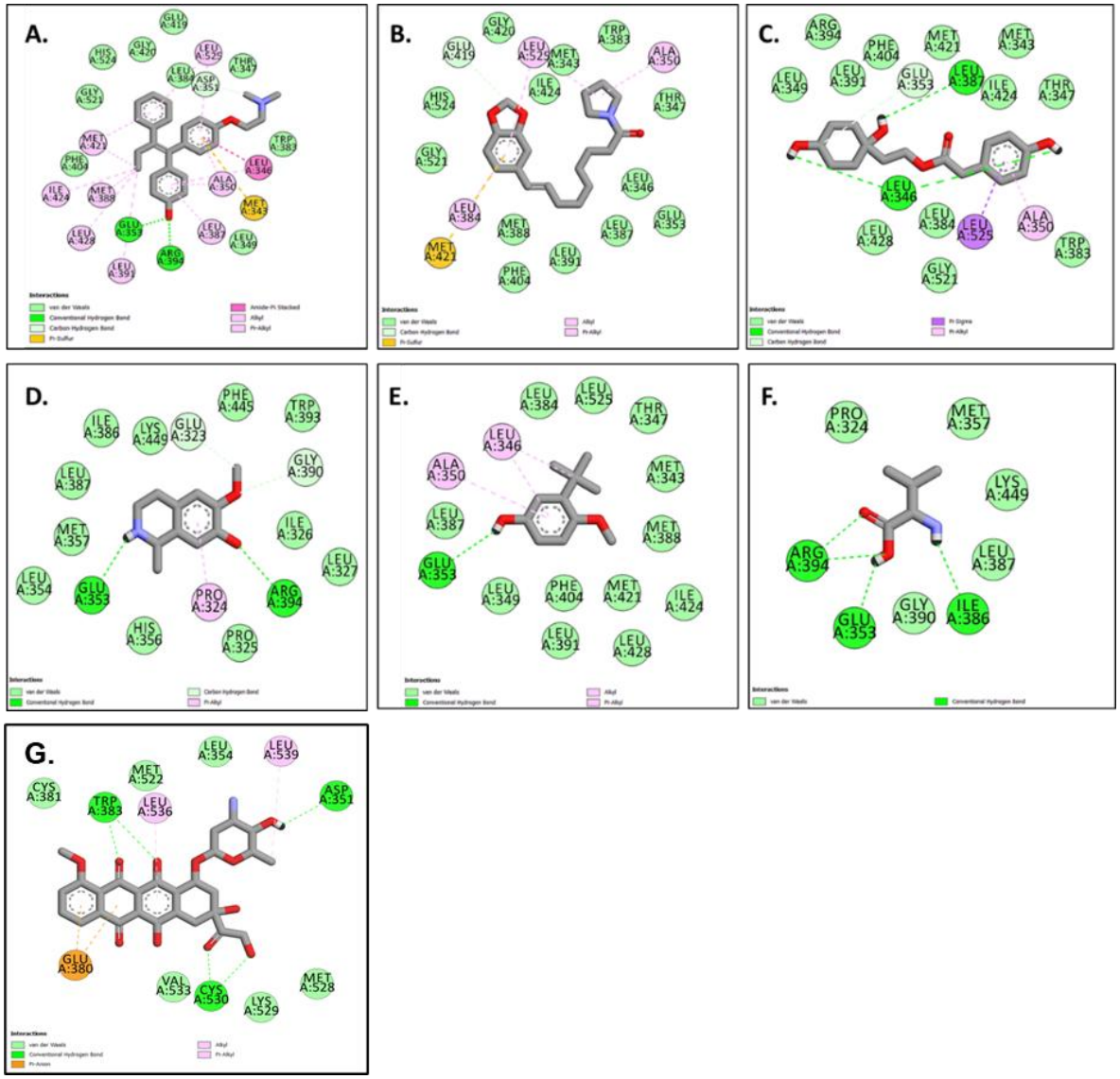

Figure 4. Molecular interactions of (**A**) HPA, (**B**) piperolactam-C9:1(8E), (**C**) rengyolester, (**D**) isosalsoline, (**E**) 3-tert-butyl-4-methoxyphenol (**F**) valine and (**G**) doxorubicin with estrogen receptor alpha (ERα).

Table 8. Molecular interactions of compounds from the hydrophilic fraction (EAE) of *Nepthea* sp. with ERα.

Compounds	Binding energy (kcal/mol)	H-bond interaction	Hydrophobic interaction
4-hydroxytamoxifen (OHT)	−9.8	Asp351, Glu353, Arg394	Leu346, Ala350, Leu387, Met388, Leu391, Met421, Ile424, Leu428, Leu525
Doxorubicin	-7.9	Asp351, Trp383, Cys530	Glu380, Leu536, Leu539
Rengyolester	−7.6	Leu346, Glu353, Leu387	Ala350, Leu525
Piperolactam-C9:1(8E)	−7.4	Glu419	Ala350, Leu382, Met421, Leu525
Isosalsoline	−6.7	Glu323, Glu353, Gly390, Arg394	Pro324
3-tert-butyl-4-methoxyphenol	−6.2	Glu353	Leu346, Ala350
Valine	−4.6	Glu353, Ile386, Arg394	–

These results correlate with the *in vitro* antioxidant performance, where **F5** (containing piperolactam-C9:1(8E) and rengyolester) exhibited stronger radical scavenging effects than **F6**. The low binding energy values and presence of multiple stabilizing interactions in F5 compounds imply effective XO inhibition potential, contributing to their free radical scavenging properties. Such interaction patterns are similar to marine-derived lactam–terpenoid hybrids previously reported to inhibit XO.

To explore the anticancer mechanism, the identified compounds were further docked into the estrogen receptor alpha (ERα) active site. The reference ligand, 4-hydroxytamoxifen (OHT), exhibited the strongest binding affinity (−9.8 kcal/mol), followed by doxorubicin, which showed a binding affinity of -7.9 kcal/mol as the control. Among the *Nepthea* compounds, rengyolester (−7.6 kcal/mol) and piperolactam-C9:1(8E) (−7.4 kcal/mol) showed the most favorable affinities, followed by isosalsoline (−6.7 kcal/mol), 3-tert-butyl-4-methoxyphenol (−6.2 kcal/mol), and valine (−4.6 kcal/mol).

Rengyolester demonstrated a close interaction profile to OHT, forming hydrogen bonds and hydrophobic contacts with Glu353, Leu346, Leu387, Ala350, and Leu525, which are crucial residues for ERα inhibition (**Figure 4**). Piperolactam-C9:1(8E) engaged in broad hydrophobic contacts with Ala350, Leu382, Met421, and Leu525, but only one hydrogen bond (Glu419). Both compounds shared key interaction residues with OHT, suggesting mimicry of the tamoxifen binding mode and potential ERα antagonistic behavior. As control, doxorubicin exhibited a distinct interaction pattern, forming hydrogen bonds with Asp351, Trp383, and Cys530, along with hydrophobic interactions involving Glu380, Leu536, and Leu539. Unlike Rengyolester and Piperolactam-C9:1(8E), doxorubicin did not significantly overlap with the key OHT-binding residues such as Glu353 and Leu525. In contrast, isosalsoline and valine formed fewer hydrogen bonds and lacked extensive hydrophobic stabilization, correlating with their weaker docking energies and minimal cytotoxic activity observed *in vitro*.

The structural similarity between rengyolester and tamoxifen, both containing aromatic and alkyl chain segments, may explain their comparable interaction networks within the ERα pocket. Furthermore, the presence of nitrogen-containing amide structures in piperolactam-C9:1(8E) supports π–π stacking and hydrogen bond formation, enhancing receptor stabilization.

The *in silico* docking outcomes closely correlate with the *in vitro* assays. Compounds from **F5**, particularly rengyolester and piperolactam-C9:1(8E), consistently displayed higher binding affinities and broader receptor interactions, paralleling the stronger cytotoxic and antioxidant activities observed experimentally. This indicates that these compounds may contribute synergistically to both antioxidant and anticancer effects via dual inhibition mechanisms—scavenging ROS through XO inhibition and suppressing ERα-mediated cancer cell proliferation.

Moreover, the alkaloid-rich nature of **F5**, supported by its LC–MS/MS profile, aligns with pharmacophoric similarities to known breast cancer therapeutics such as tamoxifen and doxorubicin, both alkaloid-based agents. Therefore, the hydrophilic fraction of *Nepthea sp.* can be considered a potential source of dual-acting marine alkaloid–terpenoid hybrids with promising antioxidant and anti–breast cancer properties.

CONCLUSIONS

This study demonstrates that the hydrophilic fractions F5 to F6 of the ethyl acetate extract of *Nepthea* sp. possess significant antioxidant and

anticancer potential. Among these fractions, F5 contains the highest levels of phenolic and terpenoid compounds, which correlate with its superior *in vitro* activity. LC–MS/MS analysis identified rengyolester and piperolactam-C9:1(8E) as the major bioactive constituents. Fraction F5 exhibited stronger radical scavenging activity, with DPPH IC_{50} of 67.39 mg/L and ABTS IC_{50} of 54.12 mg/L, as well as greater cytotoxic activity against MCF-7 cells with an IC_{50} of 42.68 mg/L, compared to F6. *In silico* studies using molecular docking supported these findings, showing that rengyolester and piperolactam-C9:1(8E) strongly interacts with xanthine oxidase and estrogen receptor alpha, with binding affinities comparable to or exceeding those of reference ligands. The results indicate that the hydrophilic fraction of *Nepthea* sp., particularly F5, is a promising source of marine natural products with dual antioxidant and anti–breast cancer activities, warranting further investigation through compound isolation and additional *in vitro* studies.

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