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Review Article

Nudibranch Bioactive Compounds for Anti-Breast Cancer Therapy: A Review and *In Silico* Studies Targeting ERα and NUDT5

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ABSTRACT

Marine mollusks, particularly nudibranchs, represent an untapped reservoir of bioactive compounds with significant potential for anti-breast cancer activity. This review consolidates and analyzes the morphology of nudibranchs, their bioactive metabolites, and the molecular mechanisms underlying their Anti-cancer effects. Additionally, it explores the *in-silico* interactions of nudibranch-derived compounds with two key targets in hormone receptor-positive breast cancer: estrogen receptor alpha (ERα) and nucleoside diphosphate-linked moiety X-type motif 5 (NUDT5). Molecular docking simulations identified ulapualide A as the most promising candidate, exhibiting strong binding affinities and stable interactions with both ERα and NUDT5, surpassing other bioactive compounds. The proposed dual-targeting mechanism of ulapualide A involves competitive inhibition of ERα by blocking estrogen binding, preventing receptor dimerization and nuclear translocation, thereby reducing the transcription of pro-cancer genes. Simultaneously, ulapualide A inhibits NUDT5 activity, which is essential for disrupting nuclear ATP production and depleting the energy supply required for ERα-driven transcription. Thus, this dual inhibition strategy represents a synergetic approach to suppressing breast cancer cell proliferation. Although the *in-silico* results are promising, additional *in-vitro* and *in-vivo* studies are essential to validate the therapeutic efficacy and safety of ulapualide A. This study underscores the potential of marine-derived compounds, particularly nudibranch metabolites, as promising candidates for targeted breast cancer therapy development and as a new avenue for oncology discovery.

Keywords: Anti-cancer, Marine mollusks, Mechanism of action, Secondary metabolites, Molecular docking.

Introduction

Cancer remains one of the leading causes of death worldwide, with nearly 10 million deaths reported in 2022. Among various cancer types, breast cancer accounts for approximately 670,000 deaths annually, underscoring the urgent need for effective therapeutic strategies.[1] While conventional therapies such as chemotherapy and radiotherapy have significantly improved survival rates, these treatments are often accompanied by severe side effects and limitations, including drug resistance and off-target toxicity. Consequently, there is growing interest in exploring alternative therapeutic approaches that offer better efficacy and safety.

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Marine biodiversity has emerged as a promising reservoir of bioactive compounds with unique chemical structures and diverse pharmacological activities. Aquatic organisms such as sea cucumbers,[2,3] sponges,[4] microalgae,[5] macroalgae,[6] and mollusks[7] Have demonstrated considerable promise as reservoirs of Anti-cancer agents. In particular, nudibranchs, a unique group of soft-bodied marine mollusks, have garnered significant attention due to their remarkable ability to produce secondary metabolites that serve as chemical defenses against predators and environmental stressors. These metabolites have been shown to exhibit potent biological activities, including Anti-cancer properties. For example, dolastatins 10 and 15, isolated from *Dolabella auricularia*, exhibit potent activity against MCF7 cell lines, which are derived from human breast cancer at nanomolar concentrations (0.06–1 nM).[8,9] Similarly, kahalalides, isolated from *Elysia rufescens*, demonstrate notable antitumor efficacy against human breast cancer cell lines SKBR3 and BT474 at micromolar doses (0.23–0.28 µM), while exhibiting minimal toxicity to non-tumor cells. Another notable compound, kulokekahilide-2, demonstrates activity against the MDA-MB-435 cell line at 14.6 nM, further reinforcing the therapeutic potential of nudibranch-derived compounds.[10,11]
Nudibranch-derived compounds offer distinct advantages over many commercial anti-cancer drugs. Their novel structural features and unique mechanisms of action enable them to circumvent common challenges such as drug resistance. For example, dolastatins disrupt

microtubule dynamics, while kahalalides induce apoptosis through membrane-disruptive mechanisms, offering alternative pathways for cancer treatment. Additionally, these compounds exhibit selective cytotoxicity against cancer cells, thereby minimizing damage to healthy tissues and reducing adverse side effects.[12] In the context of breast cancer, key molecular targets such as estrogen receptor alpha (ERα) and nucleoside diphosphate-linked moiety X-type motif 5 (NUDT5) play critical roles in disease progression. ERα drives the growth of hormone-dependent breast cancers, while NUDT5 supports cancer cell survival by regulating cellular energy metabolism. Targeting these proteins represents a strategic approach to disrupting cancer cell proliferation and survival.

This review provides a comprehensive overview of the biology of nudibranchs and critically evaluates the anti-breast cancer potential of their bioactive compound. In particular, we investigate the mechanisms of action of these metabolites by integrating insights from existing literature with in silico analyses. Molecular docking studies were conducted to elucidate the binding affinities and the interaction profiles of nudibranch-derived compounds with two key therapeutic targets in hormone receptor-positive breast cancer: ERα and NUDT5. The novelty of this review lies in its integrative methodology, which combines classical literature-based evidence with computational validation, which has not been extensively explored in previous reviews. By emphasizing both the biological relevance and therapeutic potential of nudibranch-derived compounds, this work contributes to the advancement of marine natural products in breast cancer drug discovery.

Materials and Methods

Literature Review and Compound Selection

A literature review was conducted to identify bioactive compounds derived from nudibranchs with potential anti-cancer properties. Relevant publications were collected from Google Scholar, Scopus, and PubMed up to March 2025, focusing on studies that reported the biology of nudibranchs, nudibranch-derived bioactive compounds as anti-cancer substances, the mechanism of action of nudibranch-derived bioactive compounds, and molecular docking analysis through several substances from nudibranchs for breast cancer treatment. Selected articles were critically reviewed to determine their relevance to cancer therapy.

The three-dimensional (3D) structures and structures of simplified molecular input line entry system (SMILES) of the bioactive compounds were retrieved from PubChem (Figure 2). Energy minimization was performed using YASARA software version 19.9.17 to ensure accurate molecular modeling. This step optimized atomic positions and minimized steric clashes under physiological conditions (pH 7.4), enhancing the stability of molecular conformations prior to the docking simulation.[13]

Target Protein Selection and Preparation

The molecular docking study targeted two key oncogenic proteins involved in hormone receptor-positive breast cancer: estrogen receptor alpha (ERα) (PDB ID: 3ERT, resolution: 1.90 Å) and nucleoside diphosphate 5 (NUDT5) (PDB ID: 5NWH, resolution: 2.60 Å). The 3D crystal structures of these target proteins were obtained from the Protein Data Bank (PDB). The preparation of the target protein was carried out by removing nonessential molecules, including water molecules, ions, and cofactors, to ensure accurate ligand-receptor interactions. Hydrogen atoms were added to correct bonding configurations, improving docking accuracy. All protein structures were optimized to reflect physiological conditions (pH 7.4).[14]

Simulation of Molecular Docking

The simulations were conducted to evaluate the interactions between compounds derived from nudibranchs and two control ligands: 4-hydroxytamoxifen and 7-[[5-(3,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl]methyl]-1,3-dimethyl-8-piperazin-1-yl-purine-2,6-dione (referred to as 9CH). These interactions were assessed within the binding pockets of the target proteins. 4-Hydroxytamoxifen, an active metabolite of tamoxifen, binds estrogen receptor alpha (ERα) and estrogen-driven tumor growth. In contrast, 9CH is a potent inhibitor of nucleoside diphosphate-linked moiety X-type motif 5 (NUDT5), an enzyme essential for cancer cell survival and energy metabolism. NUDT5 supports breast cancer progression by sustaining estrogen receptor signaling and supplying energy for transcriptional programs in hormone-driven cancers.[13]

The docking simulations were performed using the MacroDock platform, with 100 docking runs executed for each compound. The AMBER 14 force field was employed for the simulations, and the system was hydrated with water at a density of 0.997 g/mL. The Gasteiger charges were applied to all molecules to ensure accurate modeling of molecular electrostatic interactions. Binding energies were calculated using the VINA algorithm, which combined intermolecular contributions from the lowest-energy conformations with intramolecular energies.[13,14]

Focusing on the binding pockets, receptor grids were generated for two target enzymes: 3ERT, the human estrogen receptor alpha ligand-binding domain in complex with 4-hydroxytamoxifen, and 5NWH, representing NUDT5 bound to a potent inhibitor that silences hormone signaling in breast cancer. For 3ERT, a receptor grid measuring 30.07 Å × 30.07 Å × 30.07 Å with a spacing of 9 Å was centered on the defined binding site residues. Similarly, for 5NWH, a receptor grid measuring 31.75 Å × 31.75 Å × 31.75 Å with a spacing of 9 Å was centered on its binding site residues. The docking results were systematically analyzed and visualized to evaluate the binding interactions and conformations of the compounds.[14]

Results and Discussion

The Biology of Nudibranchs

Nudibranchs, members of the subclass *Opisthobranchia* (class *Gastropoda*), are among the most visually captivating marine invertebrates, renowned for their vibrant coloration and intricate morphological adaptations. Through evolution, these gastropods have undergone shell reduction, resulting in soft-bodied forms composed primarily of skin, muscles, and internal organs.[15] With over 3,000 identified species, nudibranchs inhabit a wide range of marine ecosystems, from shallow coral reefs to deep-sea environments exceeding 1 km in depth. Despite their striking appearance, most species typically have short lifespans, often lasting less than a year, which leads to rapid population turnover and a notable ecological impact.[16] The morphological and ecological diversity of nudibranchs is illustrated in Figure 1, which showcases specimens collected from various coral reef habitats across Indonesia, predominantly within coral rubble zones. Indonesia's rich marine biodiversity and unique environmental conditions significantly influence the distribution of these species and their production of secondary metabolites, making the region a hotspot for the discovery of bioactive compounds.

One of the most remarkable features of nudibranchs is their ability to produce and sequester secondary metabolites with potent biological activities. These bioactive metabolites, including toxins, polyketides, and peptides, serve primarily as chemical defense mechanisms against predators. Interestingly, many nudibranchs acquire these metabolites through dietary assimilation from their prey, such as sponges, bryozoans, hydroids, and ascidians, which are themselves rich sources of bioactive substances.[16,17] The chemical diversity in nudibranchs is extensive, with numerous bioactive metabolites exhibiting significant pharmacological potential, particularly as anti-cancer agents. For example, dolastatin 10, isolated from *Dolabella auricularia*, inhibits microtubule assembly and effectively suppresses cell proliferation in human cancer cell lines. Similarly, kahalalide F, a depsipeptide from *Elysia rufescens*, has been shown to impede the G0/G1 cell cycle transition in various tumor cell lines, including prostate (DU145), cervical (HeLa), colon (HT29), and head and neck (HN30) cancers.[18,19] Another promising compound, zalypsis, derived from *Jorunna funebris*, demonstrates high antitumor activity against breast, prostate, and renal cancer cells, making it a promising candidate for further drug development.[16] Active compounds from *Chromodoris sp.* have antibiotic and Anti-cancer properties[20]. Additionally, *Phyllidia coelestis* produces two cytotoxic sesquiterpenoids, 1-formamido-10(1,2)-

abeopupukeanane and 2-formamidopupukeanane, which exhibit in vitro growth inhibition against HeLa (cervical), MCF-7 (breast), KB (oral cavity), and HT-29 (colon) cancer cell lines, with IC_{50} values ranging from 0.05 to 10 µM.[21]

Dietary preferences and environmental conditions strongly influence the production and chemical diversity of these secondary metabolites. Nudibranchs that feed on bioactive-rich prey, such as sponges and ascidians, exhibit enhanced metabolite profiles with potent cytotoxic activities. For instance, *Elysia rufescens* sequesters kahalalide F from its diet of *Bryopsis spp*., while *Phyllidia varicosa* acquires cytotoxic polyketides from Porifera.[19] Environmental factors such as temperature, salinity, and habitat diversity further modulate metabolite production. Nudibranchs inhabiting coral reef ecosystems exhibit higher chemical diversity due to the abundance of chemically rich prey species. In contrast, deep-sea nudibranchs display unique metabolite profiles, potentially driven by adaptations to extreme conditions. Nudibranchs represent a prolific source of bioactive compounds with substantial biopharmaceutical potential. Their secondary metabolites exhibit diverse mechanisms of action, making them promising candidates for the discovery of anti-cancer drugs. A deeper understanding of the ecological, dietary, and environmental factors influencing their metabolite production is essential for unlocking their full therapeutic potential.

Figure 1: Morphology and biology of various species of Indonesian nudibranchs: (a) *Chromodoris annae*; (b) *Chromodoris willan*i; (c) *Doriprismatica atromarginata*; (d) *Goniobranchus kuniei*; (e) *Hypselodoris apolegma*; (f) *Nembrotha cristata*; (g) *Nembrotha kubaryana*; (h) *Nembrotha purpureolineata*; and (i) *Phyllidia ocellata.* The picture was taken by the author, located in the western part of Indonesia.

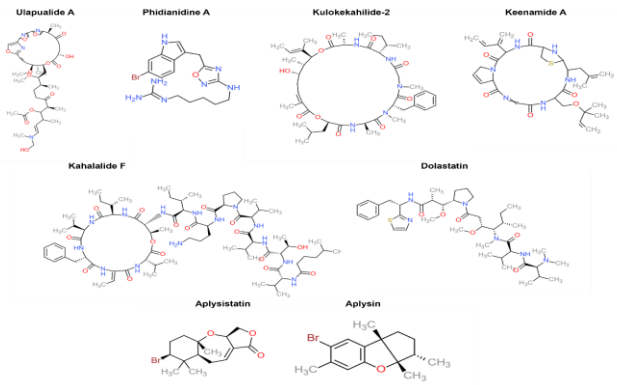

Figure 2: Chemical structure of the active compound from nudibranchs[28]

Nudibranch-Derived Bioactive Compounds as Anti-Breast Cancer Substances

Nudibranchs provide a rich source of bioactive compounds with diverse pharmacological applications, including anti-cancer activity. Several notable compounds have been identified, such as dolastatins (10 and 15), kahalalides (A and F), keenamide A, phidianidine, aplysistatin, ulapualide A, and various alkaloids and steroids. These compounds exhibit unique mechanisms of action, potent anti-cancer activities, and significant promise for drug development. Chemical structures of the nudibranch-derived bioactive compound are shown in Figure 2.

Dolastatins: Potent Anti-cancer Peptides

Dolastatins constitute a family of pentapeptides isolated from the sea slug *Dolabella auricularia* and cyanobacteria species, including *Lyngbya sp.*, *Symploca sp.*, and *Symploca spp.* These compounds exhibit remarkable Anti-cancer properties by disrupting mitosis and inhibiting cell division, making them promising candidates for cancer therapy. Among the most potent dolastatins are dolastatin 3, 10, 11, 12, 13, 15, G, and H. Dolastatin 10 (Dol-10) and dolastatin 15 (Dol-15) demonstrate significant Anti-cancer potential due to their distinctive mechanisms of action. Dol-10 and Dol-15 induce apoptosis in various cancer cells, even at low nanomolar concentrations, by binding to β-tubulin, altering the expression of specific cancer-related proteins, causing the loss of telomeric sequences in chromosomes, and triggering chromosomal abnormalities, all of which contribute to their potent antitumor effects.[8]

The therapeutic potential of Dol-10 has led to the development of an enhanced antitumor activity. For instance, TZT-1027 (Soblidotin), a Dol-10, progressed to Phase I clinical trials, exhibiting promising anti-cancer effects. However, dose-limiting toxicities, such as neutropenia and inadequate dosage levels, hindered its clinical efficacy.[9,22] Another Dol-10 derivative, monomethyl auristatin E (MMAE), has shown remarkable clinical success. MMAE is conjugated with a monoclonal antibody to form Adcetris® (Brentuximab vedotin), which was approved by the FDA in 2011 for the treatment of anaplastic large T-cell systemic malignant lymphoma and Hodgkin lymphoma.[23] The conjugation of MMAE with monoclonal antibodies improves targeted drug delivery, minimizing off-target toxicity while enhancing antitumor activity. Dol-10 has also been investigated as a first-line and second-line chemotherapy for advanced breast cancer, but clinical trials revealed no significant antitumor activity. Nevertheless, the compound exhibited hematological toxicity within an acceptable range. It has been hypothesized that higher doses of Dol-10 might overcome its drug resistance and enhance its anti-tumor efficacy.[24]

Dol-10 has demonstrated substantial *in vitro* and *in vivo* anti-cancer activity. For example, it effectively inhibits the growth of MCF-7 breast cancer cells, with an IC_{50} of 0.036 µg/mL.[25] In murine models, therapeutic doses of Dol-10 were reported to be 1350 µg/m² in mice (450 µg/kg), 450 µg/m² in rats (75 µg/kg), and ≤400 µg/m² in dogs (≤20 µg/kg). Similarly, Dolastatin 15, when conjugated with Trastuzumab, exhibited enhanced cytotoxicity against SK-OV-3 ovarian cancer cells and MDA-MB-231, MCF-7, and SK-BR-3 breast cancer cells, with IC50 values of 1.5 nM and 2.6 nM, respectively. In SCID mice, Dol-15 (at 20 mg/kg) significantly reduced tumor growth and volume.[26]

Synthetic derivatives of Dol-10, such as TZT-1027, have also demonstrated enhanced efficacy against chemotherapy-resistant tumors. TZT-1027 exhibited superior activity against cisplatin-resistant P388 cells, with moderate activity against 5-fluorouracil- and vincristine-resistant P388 cells, but limited efficacy against adriamycin-resistant P388 cells. In human xenograft models, TZT-1027 significantly regressed tumors in mice bearing MX-1 breast and LX-1 lung carcinomas. In clinical trials, Dol-10 was administered as an intravenous bolus in 94 cycles at doses ranging from 65 to 455 µg/m². The maximum tolerated dose (MTD) was established at 400 µg/m² for patients with minimal prior treatment and 325 µg/m² for heavily pretreated patients.[9] Although Dol-10 was used as a first-line and second-line therapy for metastatic breast cancer, the results showed no significant antitumor activity. Still, the drug remained well-tolerated at hematologically acceptable levels. It was proposed that higher doses of Dol-10 might overcome its resistance and exhibit more potent anti-

cancer effects.[27] The schematic mechanisms of dolastatins and their isoforms against breast cancer are illustrated in Figure 3.

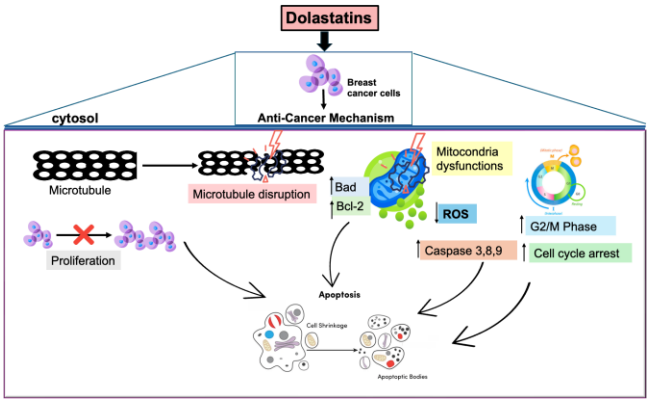

Figure 3: Schematic representation of the key anti-breast cancer mechanisms of dolastatins and their analogues. Dolastatins exert their Anti-cancer effects by disrupting microtubule dynamics, thereby inhibiting cell proliferation, inducing apoptosis, and triggering chromosomal abnormalities.[9] These compounds also promote cell cycle arrest and interfere with tumor growth pathways, making them promising candidates for cancer therapy. *Figure created using PowerPoint*.

Kahalalides

Kahalalides are a class of cyclic depsipeptides initially isolated from the sacoglossan mollusk, *Elysia rufescens*, and its dietary algae, *Bryopsis spp*. These compounds have since been identified in several sarcoglossans across the globe, including *E. ornata* and four related candidate species from the Indo-Pacific region. Other potential kahalalide-producing species, such as *E. tomentosa* and *E. grandifolia*, have also been proposed as sources of these bioactive peptides.[18,28] To date, 16 cyclic depsipeptides have been isolated from *Bryopsis spp.* and *E. rufescens*, including kahalalides A-F, K, O, P, Q, R, and S, along with three acyclic derivatives (kahalalides G, H, and J). Four additional kahalalides (V, W, X, and Y) have been exclusively identified in *E. rufescens*[18]. Notably, Kahalalide F (KF) has undergone extensive derivatization, resulting in over 200 known variants, though only two modifications of the singular ornithine residue have demonstrated bioactivity equal to or greater than that of the parent compound.[29]

Kahalalide F is the most representative and biologically potent compound of this group. It is a C75 tridecapeptide that exhibits significant in vitro and in vivo antitumor activity against various human solid tumors, including breast, prostate, non-small cell lung (NSCLC), ovarian, liver, and colon carcinomas.[28,30] Preclinical studies revealed that KF's anti-cancer efficacy is associated with ErbB3 (HER3) expression and inhibition of the PI3K-Akt signaling pathway, vital for cancer cell proliferation and survival. KF demonstrates remarkable potency against prostate (IC_{50}: 0.07 - 0.28 µM) and breast cancer cell lines (SKBR-3, BT474, MCF7) with IC_{50}: 0.28 µM.[31] Interestingly, unlike most conventional anti-cancer agents, KF does not induce apoptosis. Instead, it kills cancer cells through necrosis or oncosis, characterized by cell swelling, vacuole formation, and disintegration of the lipid bilayer, ultimately leading to cell membrane rupture and detachment. This is accompanied by liposomal lysis and a detectable release of free fatty acids, further compromising cell integrity.

The anti-cancer mechanism of KF is partially attributed to its ability to downregulate ErbB3, a member of the epidermal growth factor receptor (EGFR) family. Although ErbB3 lacks intrinsic kinase activity, it heterodimerizes with ErbB2 (HER2), particularly in HER2-overexpressing tumors, to activate pro-proliferative and pro-survival signaling cascades, including the MAPK, PI3K/Akt, and JAK/STAT pathways.[32] This heterodimerization is a major driver of 20–25% of breast cancers, with ErbB3 also overexpressed in estrogen receptor-positive and luminal breast tumors, colon, and gastric cancers, where it plays a key role in tumor cell survival.[33]

KF's ability to inhibit ErbB3 signaling makes it particularly effective against ErbB3-overexpressing breast, colon, lung, vulvar, and hepatic cancer cell lines[18]. Furthermore, ErbB3 frequently forms heterotrimeric complexes with ErbB2 and IGF-1R (insulin-like growth factor 1 receptor), contributing to resistance against HER2-targeted therapies, such as Herceptin (trastuzumab), and hormonal treatments like tamoxifen.[34] By downregulating ErbB3, KF disrupts these resistance mechanisms, highlighting its potential in overcoming therapeutic resistance in HER2-positive and EGFR-targeted cancers. Overall, kahalalides, particularly KF, represent a promising class of marine-derived anti-cancer agents with potent activity against multiple solid tumors and the potential to overcome resistance to conventional therapies, making them valuable candidates for further clinical development.

Keenamide A

Keenamide A, a cyclic hexapeptide isolated from the notaspidean mollusk *Pleurobranchus forskalii*, has demonstrated significant cytotoxic activity against various cancer cell lines, including P-388 (murine lymphocytic leukemia), A-549 (human lung carcinoma), MEL-20 (melanoma), breast cancer (MDA-MB-231, MCF-7),and HT-29 (human colon adenocarcinoma).[35,36] The chemical structure of Keenamide A is cyclo-[Gly-Ser(Unk)-Unk-xiIle-Pro],[37] and it exhibits potent cytotoxicity, with reported IC_{50} values of 2.5 µg/mL against P-388, A-549, and MEL-20 cell lines and 5.0 µg/mL against HT-29 cells.[35] Despite its promising anti-cancer effects, the exact mechanism of action (MoA) of Keenamide A remains unidentified. However, its cytotoxicity may involve various mechanisms, such as induction of apoptosis, inhibition of cell proliferation, or disruption of key cellular signaling pathways, including the PI3K/AKT/mTOR or MAPK pathways, which are often dysregulated in cancer.[35,37]

Phidianidine and Other Alkaloids

Phidianidine A is a distinctive indole alkaloid isolated from the aeolid opisthobranch *Phidiana militaris*. It features an uncommon 1,2,4-oxadiazole ring system linked to a brominated indole structure, placing it within a class of compounds known for their antifouling activity. Its structure is highly analogous to other marine-derived compounds such as ianthelline, barettin, and synoxazolidinones, which are similarly associated with potent bioactivity, including antifouling and cytotoxic effects.[38] Early studies of phidianidine A revealed its cytotoxic properties, and more recent investigations have further highlighted its immunosuppressive effects, adding to its therapeutic potential.[39] Additionally, phidianidine A has been identified as a selective inhibitor of the dopamine transporter and a potent ligand and partial agonist of the µ-opioid receptor, showing significantly higher affinity for this receptor than δ- and κ-opioid receptors.[28]

Furthermore, virtual screening followed by experimental validation has revealed that phidianidine A acts as a CXCR4 antagonist, a chemokine receptor associated with several pathologies, including HIV, rheumatoid arthritis, and cancer.[38] CXCR4 plays a critical role in cancer metastasis, and its inhibition by phidianidine A may offer therapeutic strategies for targeting metastasis in various cancers. Indeed, phidianidine A significantly reduced CXCL12-induced migration in a rat pituitary adenoma cell line at concentrations of 50 µM, underscoring its potential in treating metastatic diseases.[12]

Phidianidine A and its analogues also display selective cytotoxicity across several cancer cell lines, with GI_{50} values ranging from approximately 0.4 to >100 µM in three different cancer cell lines, including C6 glioma, HeLa cervical cancer, breast cancer, and Caco-2 colon cancer cells. Interestingly, the compounds show no significant selectivity for mouse 3T3-L1 fibroblasts and rat H9C2 cardiomyocytes, indicating that they are not nonspecific poisons.[28] Moreover, human HeLa cells exhibit increased sensitivity to the growth-inhibitory effects of phidianidines compared to Caco-2 cells, suggesting distinct mechanisms of action between different tumor types.[39]

In addition to their Anti-cancer properties, phidianidines A and B also exhibit partial agonist activity at the µ-opioid receptor, which has been implicated in cancer progression and pain management.[28] This dual activity could make phidianidine A an attractive candidate for further

investigation as a multitarget drug capable of addressing both the cancer and pain aspects of oncology. Furthermore, the ability of phidianidines to act as potent ligands of CXCR4, a receptor integral to the immune system and cancer metastasis, further supports their therapeutic potential, particularly in the treatment of metastatic cancer.[21]

Aplysistatin and Ulapualide

The 2-propanol extract of the sea hare *Aplysia angasi* (also known as *A. dactylomela*) has demonstrated significant growth-inhibitory activity against murine lymphocytic leukemia P388 cells.[28] The active compound responsible for this activity, aplysistatin, was isolated through bio-guided fractionation. Aplysistatin is a brominated tricyclic sesquiterpene featuring a unique 6-7-5 fused ring system. This structure includes a seven-membered ring containing a bridging oxygen atom and a five-membered lactone ring. The compound exhibited growth inhibition (GI_{50}) values of approximately 8 μM against both human KB oral cancer cells (which are cross-contaminated by HeLa cervical carcinoma cells) and mouse P338 leukemia cells.[28] This highlights aplystatin as a promising candidate for further exploration in cancer therapeutics.

In addition to *Aplysia angasi*, other species of the *Aplysia* genus, including *A. depilans*, *A. fasciata*, *A. juliana*, *A. kurodai*, *A. oculifera*, and *A. punctata*, have been investigated for their bioactive metabolites. The broad chemical diversity found in these species is primarily attributed to the marine algae and cyanobacteria they consume, which serve as sources of many bioactive compounds.[39] Notably, aplysistatin has been shown to exhibit growth-inhibitory effects on several other cancer cell lines, including HM02 gastric carcinoma, HEP-G2 liver carcinoma, and MCF-7 breast carcinoma, with IC50 values of around one μM.[21] Further supporting its broad-spectrum anti-cancer potential.

While aplysiastatin is a vital compound derived from *Aplysia angasi*, it represents only one example of the wealth of bioactive metabolites produced by marine organisms in this genus. Other noteworthy compounds include ulapualides A and B, C-E, which were isolated from the red-colored egg masses of the nudibranch *Hexabranchus sanguineus*.[40] These compounds are believed to function as chemical defenses against the predator, *Favorinus japonicus*, the only known predator of *Hexabranchus sanguineus*. Ulapualides are characterized by their three contiguous oxazole rings, which form part of a macrolide ring structure, with a lipid-like side chain terminating in an N-methyl-N-alkenylformamide group[21].

Both ulapualides A and B have demonstrated potent cytotoxic activity, with GI_{50} values of approximately 10 nM and 30 nM, respectively, against murine L1210 leukemia cells and breast cancer. Ulapualide A, in particular, has also been shown to possess actin-depolymerizing activity, which could explain its Anti-cancer effects by disrupting the cytoskeleton in rapidly dividing tumor cells.[41] Moreover, ulapualide A has been isolated from other marine sources, including sponges, further indicating its widespread occurrence in aquatic ecosystems. The total synthesis of ulapualide A was achieved in 1998, paving the way for the development of synthetic analogues and further exploration of its potential as an anti-cancer agent.[28]

Steroids and Proteins with Antiproliferative Effects

Steroids isolated from *Aplysia dactylomela* exhibit antiproliferative effects on gastric (HM02), liver (HepG2), and breast cancer (MCF-7) cell lines, with IC_{50} values of approximately 3 μM.[21,28] Similarly, proteins from *Aplysia sp.* have been shown to have inhibitory effects on NB4 cancer cells. For example, dendrodoristerol, a steroidal compound isolated from the Vietnamese nudibranch mollusk *Dendrodoris fumata*, demonstrates notable *in vitro* cytotoxicity against six human cancer cell lines: HL-60, KB, LU-1, MCF-7, LNCaP, and HepG2. The compound exhibited half-maximal inhibitory concentration (IC_{50} values of 21.63, 22.22, 24.53, 41.19, 25.34, and 21.59 μM. While these values are higher compared to the standard chemotherapeutic agent ellipticine (IC_{50} values: 1.91, 1.42, 1.79, 2.32, 1.34, and 1.50 μM, respectively), dendrodoristerol still represents a promising lead for further modification and study.[42] The bioactive compounds from nudibranchs and their anti-cancer activities against breast cancer are summarized in Table 1.

Molecular Docking Targeting ERα and NUDT5 as a Model Anti-Breast Cancer Therapy

Considering the potential of bioactive compounds derived from nudibranchs as anti-breast cancer agents, we investigated their potential therapeutic effects against breast cancer through molecular docking simulations. The aim was to evaluate their binding affinities toward estrogen receptor alpha (ERα) and nucleoside diphosphate-linked moiety X-type motif 5 (NUDT5), two critical targets associated with breast cancer progression.

Eight nudibranch-derived compounds with reported anti-breast cancer activity were selected: Aplysistatin, Ulapualide A, Kahalalide F, Aplysin, Phidianidine A, Dolastatins, Kulokekahilide-2, and Keenamide A. Two control ligands were included for comparison: 4-hydroxytamoxifen (OHT) for ERα and 7-[[5-(3,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl]methyl]-1,3-dimethyl-8-piperazin-1-yl-purine-2,6-dione (9CH) for NUDT5. The docking simulations assessed the binding energies and molecular interactions, with lower docking scores indicating stronger binding affinities.

ERα plays a crucial role in breast cancer, as it regulates transcriptional pathways involved in cell proliferation and survival. Dysregulation of ERα promotes oxidative stress through cytochrome P450 1B1 (CYP1B1), accelerating neoplastic transformation.[43] Meanwhile, NUDT5, an ADP-ribose pyrophosphatase, acts as a co-regulator of ERα signaling. Overexpression of NUDT5 is strongly associated with poor prognosis in breast cancer patients, making it a promising therapeutic target. [44,45] Table 2 summarizes the docking scores of the nudibranch-derived compounds compared to the control ligands. Ulapualide A demonstrated the most favorable binding affinities among the tested compounds, with docking scores of -8.372 kcal/mol for ERα and -8.000 kcal/mol for NUDT5. However, none of the nudibranch-derived compounds surpassed the control ligands' binding efficiency. Interestingly, all nudibranch-derived compounds exhibited stronger binding affinities toward NUDT5 than OHT, highlighting their potential as inhibitors of this enzyme. 9CH demonstrated the highest overall binding affinity for both ERα and NUDT5, confirming its role as an effective control ligand.

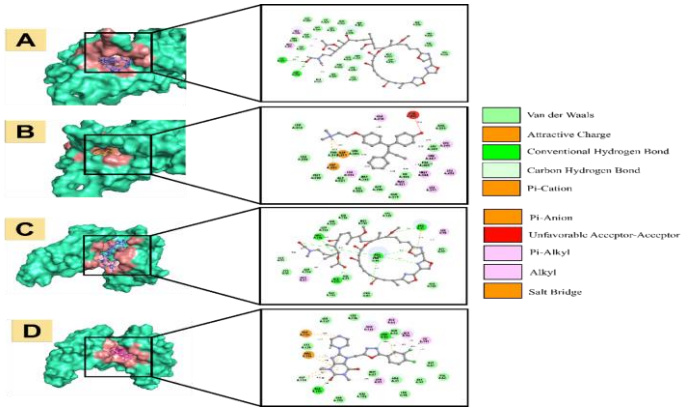

Figure 4: Docking pose and interaction: A. Ulapualide A-ERα; B. OHT-ERα; C. Ulapualide A-NUDT5; D. 9CH-NUDT5.

ERα Binding Affinity

Ulapualide A exhibited a binding profile within the ERα pocket similar to that of OHT. Although its binding energy was slightly lower than OHT's, Ulapualide A established three additional hydrogen bonds with Leu387, Arg394, and Glu353, which were absent in the OHT interaction (Figure 4). These hydrogen bonds may enhance the stability of the ligand-receptor complex, despite the slightly weaker overall binding affinity, especially considering that OHT showed a repulsive acceptor-acceptor interaction potentially destabilizing the ERα binding site.[46] These findings suggest, despite a lower binding energy, ulapualide A could provide greater stability and improved efficacy in modulating ERα function, enhancing its anti-cancer activity.

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Table 1: Bioactive compounds from nudibranchs and their anti-breast cancer activities

No	Compound	Class	Species	Anti-cancer Activity	Doses	Mechanism of Action	References
1	Kulokekahilide-2	Cyclic depsipeptide	*Philinopsis speciosa*	Cytotoxic against MDA-MB-435 and A-10 cells	4.2 to 59.1 nM	Induces apoptosis and disrupts mitochondrial function	10,11
2	Keenamide A	Peptide	*Pleurobranchus forskalii*	Cytotoxic against P-388 leukemia, breast cancer, and A-549 adenocarcinoma cells	IC_{50} = 5.0 µg/ml	Induces apoptosis, inhibits cell proliferation, and disrupts PI3K/AKT/mTOR and MAPK pathways	35,36,37
3	Dolastatins	Peptide	*Dolabella auricularia*	Cytotoxic against breast and liver cancer, solid tumors	450 µg/kg (mice), 450 µg/m² (humans), 75 µg/kg (rats), ≤400 µg/m² (dogs)	Inhibits mitosis by disrupting tubulin polymerization and GTP hydrolysis, induces apoptosis, promotes cell cycle arrest, and interferes with tumor growth pathways	9,26
4	Kahalalide F	Peptide	*Elysia rufescens*	Cytotoxic against prostate, liver, and breast cancer cells	0.07–0.28 µM (PC3, DU145, LNCaP), 28 µM (SKBR3, BT474, MCF7), 0.3 µM (HepG2)	Induces necrosis via lysosomal disruption, inhibits PI3K–AKT signaling, downregulates ErbB3, disrupts EGFR signaling, and promotes vacuolization leading to cell death	18,30,33
5	Phidianidine A	Alkaloid	*Phidiana militaris*	Cytotoxic against adenoma cell line	50 µM	Reduces CXCL12-induced migration in rat pituitary cells, inhibiting metastasis	39
6	Unidentified Active Compound	Terpenes & Steroids	*Aplysia dactylomela*	Cytotoxic against HM02 (gastric carcinoma), HEP-G2 (liver carcinoma), and MCF-7 (breast carcinoma)	3 µM	Binds to DNA, causing cytotoxicity	21
7	Aplysin	Protein	*Aplysia kurodai*	Inhibitory effects on various cancer cell lines	4 and 8 µM	Modifies cell membrane lipids, exhibiting antineoplastic activity	28
8	Aplysistatin	Protein	*Aplysia angasi*	Cytotoxic against murine lymphocytic leukemia P338,	8 µM, one µM	Sensitizes TRAIL-induced apoptosis and enhances alkylating drug cytotoxicity	28,39

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				P388, and breast and oral cancer cells			
9	Dendro-doristerol	Steroid	*Dendrodoris fumata*	Cytotoxic against MCF-7 breast cancer cells	2.32 μM	Induces apoptosis and inhibits cell proliferation	42
10	Ulapualide-A	Macrolide	*Hexabranchus sanguineus*	Cytotoxic against L1210 (murine leukemia) and breast cancer cells	10 nM, 30 nM	Disrupts cytoskeletal structures in rapidly dividing tumor cells, leading to mitotic arrest	21,4128

Table 2: Docking Simulation of nudibranch-derived compounds against ERα and NUDT5

Compound	**Class Compound**	**ERα** Binding Energy (kcal/mol)	**Rank**	**NUDT5** Binding Energy (kcal/mol)	**Rank**	**Average Binding Energy (kcal/mol)**	**Average Ranking (2)**
4-hydroxytamoxifen	Control drug	-10.021	1	-6.685	10	-8.353	5.5
7-[[5-(3,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl]methyl]-1,3-dimethyl-8-piperazin-1-yl-purine-2,6-dione	Control drug	-9.267	2	-8.189	1	-8.728	1.5
Aplysistatin	Protein	-8.409	3	-7.211	6	-7.810	4.5
Ulapualide A	Macrolide	-8.372	4	-8.000	2	-8.186	3
Kahalalide F	Peptide	-8.121	5	-7.803	3	-7.962	4
Aplysin	Protein	-7.900	6	-6.876	9	-7.388	7.5
Phidianidine A	Alkaloid	-7.772	7	-7.325	5	-7.549	6
Dolastatins	Peptide	-7.609	8	-6.921	8	-7.265	8
Kulokekahilide-2	Cyclic depsipeptide	-7.508	9	-7.204	7	-7.356	8
Keenamide A	Peptide	-6.956	10	-7.480	4	-7.218	7

NUDT5 Binding Affinity

Ulapualide A exhibited distinct interactions compared to 9CH. Unlike 9CH, which interacted with six key residues (Gly61, Val62, Ala63, Ala96, Ile141, and Thr192) (Figure 4), ulapualide A engaged fewer residues, interacting with 20 amino acids. However, it formed five hydrogen bonds, one more than 9CH, which may indicate stronger localized interactions with NUDT5 despite a smaller overall interaction footprint. These findings suggest ulapualide A could offer an effective inhibitory action on NUDT5, potentially modulating the enzyme's role in enhancing ERα signaling and contributing to cancer progression. While the docking simulations reveal that ulapualide A shows the most promising binding affinities among the nudibranch-derived compounds, none surpassed the control ligands in overall docking efficiency. However, the stronger binding affinity of these compounds toward NUDT5 indicates their potential as novel inhibitors of this enzyme, warranting further experimental validation. The future steps should involve *in-vitro* and *in-vivo* studies to further validate these results and assess the therapeutic potential of ulapualide A and other nudibranch-derived compounds in breast cancer therapy, with a particular focus on their ability to modulate ERα and NUDT5 signaling pathways.

Potential Inhibitory Mechanism of Action of Ulapualide A Against ERα and NUDT5 in Breast Cancer

Estrogen receptor alpha (ERα) is a key driver of hormone receptor-positive breast cancer, accounting for approximately 70% of cases and representing a critical therapeutic target. Under physiological conditions, estrogen (E2) binds to the ligand-binding domain (LBD) of ERα, inducing conformational changes that promote receptor dimerization.[47,48] The ERα homodimer translocates into the nucleus, where it binds to estrogen response elements (ERE) on target gene promoters, recruiting coactivators and transcription factors. This process drives the transcription of oncogenic genes such as *Cyclin D1*, leading to uncontrolled cell proliferation.[49,50] Docking simulations revealed ulapualide A acts as a competitive ERα inhibitor by binding to the same LBD pocket as OHT. Ulapualide A exhibited strong interactions with key ERα residues, including Met343, Leu346, Thr347, Leu349, Ala350, Asp351, Glu353, Trp383, Leu384, Leu387, Leu391, and Arg394. Its binding profile closely resembled that of OHT but included additional hydrogen bonds with Leu387, Arg394, and Glu353, enhancing complex stability. Despite a slightly weaker binding energy than OHT, these extra hydrogen bonds may strengthen the overall interaction, potentially suppressing ERα-driven transcriptional activity and mitigating breast cancer progression.

NUDT5 is involved in nuclear ATP production, essential for chromatin remodeling and transcriptional regulation. During estrogen signaling, NUDT5-generated ATP powers the ERα transcriptional machinery, driving the expression of genes that promote proliferation. Overexpression of NUDT5 enhances ERα transcriptional activity, making it a promising target for breast cancer therapy.[44] Docking studies demonstrated that ulapualide A interacts with key NUDT5 residues, forming five hydrogen bonds, one more than 9CH, suggesting more potent localized inhibition. Although ulapualide A exhibited slightly higher binding energy than 9CH, its enhanced hydrogen bonding network may disrupt NUDT5's catalytic activity, thereby reducing nuclear ATP production. This energy depletion weakens ERα-driven transcription, thereby suppressing oncogenic gene expression and slowing the progression of breast cancer.[48,51] The dual-targeting mechanism of ulapualide A offers a synergistic therapeutic effect by simultaneously inhibiting ERα and NUDT5 (Figure 5)

ERα Inhibition

Ulapualide A competes with estrogen for ERα binding, blocking receptor dimerization and nuclear translocation. This reduces ERα-mediated transcription of pro-cancer genes, slowing breast cancer progression.

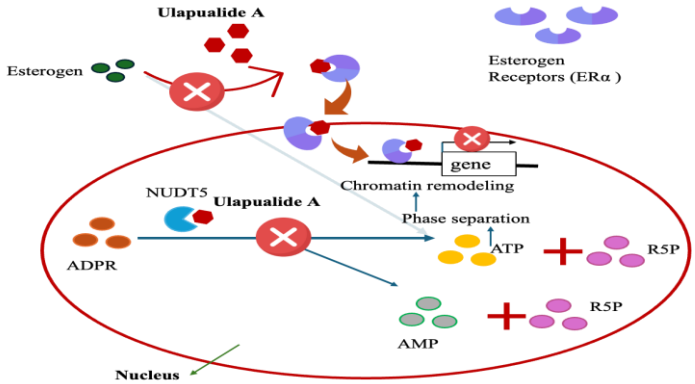

Figure 5: Potential inhibitory mechanism of action of ulapualide A against ERα and NUDT5 in breast cancer. Ulapualide A competes with estrogen for binding to ERα, preventing receptor dimerization and nuclear translocation, and subsequently reducing ERα-mediated transcription of oncogenic genes. Simultaneously, ulapualide A inhibits NUDT5 activity, impairing nuclear ATP production. This energy depletion limits the transcriptional capacity of ERα, thereby further suppressing the expression of genes involved in proliferation, highlighting the potential for a dual-target therapeutic strategy against breast cancer. *Figure created using PowerPoint.*

NUDT5 Inhibition

Ulapualide A restricts the energy supply for ERα-driven transcription by inhibiting nuclear ATP production, thereby further reducing oncogenic gene expression.

This dual-inhibition strategy enhances anti-cancer efficacy by disrupting both upstream receptor activation and downstream transcriptional machinery, potentially reducing the likelihood of resistance development. These results highlight ulapualide A's potential as a dual-target therapeutic agent, warranting further structural optimization to enhance binding affinity, pharmacokinetics, and overall therapeutic efficacy.

Conclusion

Nudibranchs represent an underexplored yet highly promising reservoir of bioactive compounds with significant Anti-cancer potential. Although marine-derived Anti-cancer agents currently occupy a limited role in existing therapeutic regimens, compounds such as dolastatin, ulapualide A, keenamide, aplysistatin, kahalalide F, kulokekahilide-2, and phidianidine have demonstrated remarkable Anti-cancer activities with various mechanisms of action. These compounds primarily exert their effects by targeting tubulin, inhibiting cell proliferation, and stabilizing microtubules — mechanisms comparable to those of established chemotherapeutic agents. Such evidence positions nudibranchs as a valuable resource for discovering novel Anti-cancer agents. Through molecular docking studies, we specifically identified ulapualide A as a promising candidate for breast cancer therapy, highlighting its potential as a dual-target inhibitor of ERα and NUDT5. These findings provide a strong foundation for the development of targeted treatment strategies for hormone receptor-positive breast cancer. Nonetheless, further *in vitro* and *in-vivo* investigations are necessary to confirm the therapeutic potential, target specificity, and safety profile of ulapualide A.

Conflict of Interest

The author`s declares no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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