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Review

Molecular Insights into Marine Sponge-Derived Bromotyrosine Alkaloids: Emerging Therapeutic Perspectives against Triple-Negative Breast Cancer

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Abstract

Triple-negative breast cancer (TNBC) ranks as one of the most deadly and difficult-to-treat types of carcinomas of the breast, distinguished by the absence of oestrogen & progesterone receptors, as well as HER2. Therefore, therapies are constrained and present hormonal and targeted therapies are ineffective. Results of chemotherapy are subpar over the long term, and this underlines the acute necessity of innovative treatments. Recent research in marine natural products such as the bromotyrosine alkaloids found in marine sponges, however, has sparked interest in oncology, as they are characterized by their extraordinary chemical diversity and multitargeted biological activity. Their uniqueness as brominated scaffolds due to the presence of apoptotic properties allows both apoptotic control and cell cycle and epigenetic regulation. In this review, there is a need to initiate a consistent pharmacognostic endeavor to investigate bromotyrosine alkaloids through organized extraction techniques, elucidations of chemical structures and thorough biological characterization. Recent developments such as analytical discoveries, bioassay-guided isolation, and some new formulation approaches are outlined, along with preclinical efficacy and safety information. The findings suggest that TNBC has considerable therapeutic potential, with the potential of clinical translation of the findings and suggests that interdisciplinary research plays important role in providing direction to the development of these compounds. The results support the radical value of bromotyrosine alkaloids and promote the practical development to the next generation of oncological drugs.

Keywords

Bromotyrosine, Marine alkaloids, Natural, Pharmacognosy, Progesterone, Triple-negative breast cancer

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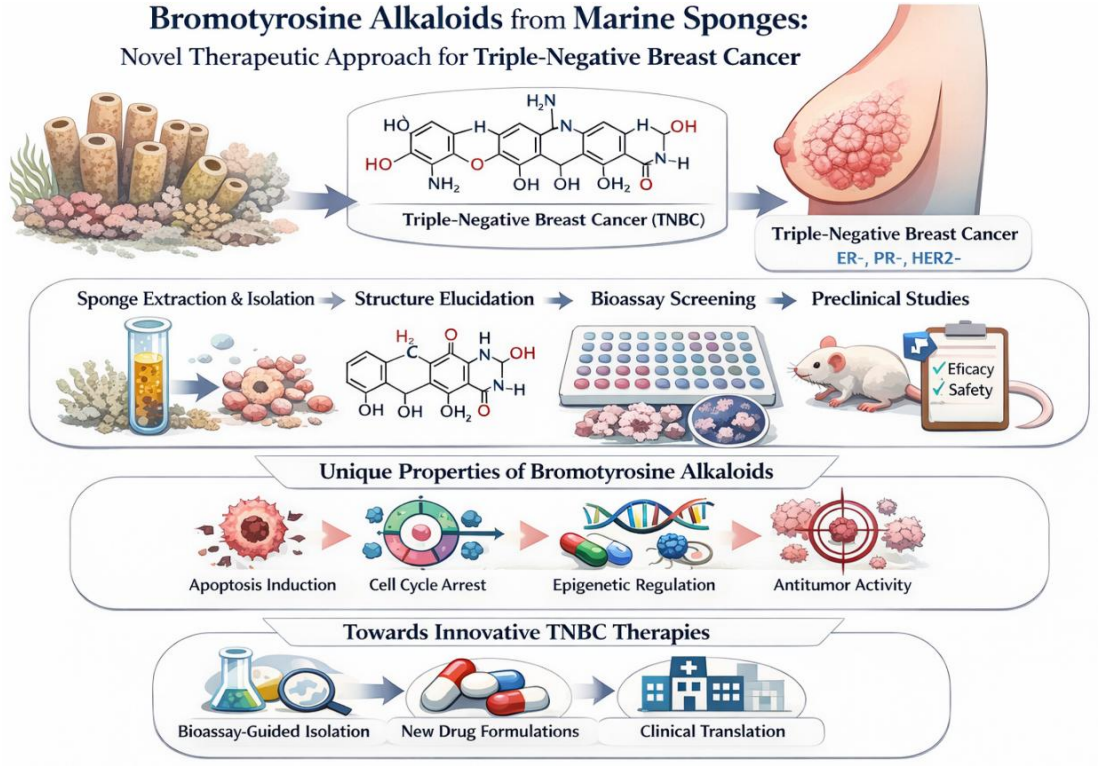
Graphical Abstract



1. Introduction

Triple-negative breast cancer (TNBC) is a type of breast cancer that is highly malignant which forms about 10 to 15 percent of the total number of breast cancer victims in the globe [1]. Being characterized by a lack of oestrogen, progesterone, and HER2 receptors, TNBC has a disproportionately high prevalence in younger females and certain ethnic groups and is systematically associated with dismal clinical outcomes [2]. The TNBC cases recorded worldwide in 2022 presumably happened to be 300,000 cases, and Asia was the heaviest burdened continent followed by Europe and North America [3]. Resistance to existing targeted therapies is also greatly observed in this subtype of cancer leaving chemotherapy as the main strategy of treatment though still with low lasting effectiveness and relapse rates [4]. The rising rate of incidences and difficulty in treating them is why there is an urgent need to develop new effective therapeutic interventions in order to enhance survival and quality of life of the patient [5]. The comparison of conventional TNBC therapies *vs.* marine-derived compounds is shown in Table 1.

Table 1. Comparison of conventional TNBC therapies *vs*. marine-derived compounds.

Therapy Type	Examples	Mechanism of Action	Clinical Application Status	Key Advantages	Ref.
Conventional Therapies	Bernoulli Approaches doxorubicin (DOXO)/ Taxane; DOXO/carboplatin; Taxane/ carboplatin (AG); and Platinum regimen System	Standard Treatments; Cytotoxic chemotherapy causes DNA damage and lead to mitotic arrest; surgery eliminates the tumor; radiation kills the local cells	Standard of care; first-line and adjuvant	Well-established protocols, broad efficacy, but high relapse and toxicities; limited effectiveness in advanced stages.	[6]
Targeted Therapy/ Immunotherapy	Pembrolizumab (immunotherapy), PARP inhibitors Olaparib	Immunotherapy blocks PD-1/PD-L1 to restore immune response; PARP inhibitors block DNA repair in BRCA-mutated tumors	Used for PD-L1+ cases, BRCA-mutations	Advances outcomes in select patients; immunotherapy has immune-related adverse events, limited to subgroups.	[7]
Marine-Derived Compounds	Plocabulin, Eribulin, Trabectedin, Lurbinectedin (Tunicate derived), Auristatin based ADCs, Crambescidin 800 (*Monanchora viridis*), Batzellines, Coibamide A (cyanobacteria)	Microtubule poisons, DNA minor groove binders, apoptosis inducers, immunomodulators, vascular disrupting agents	Mostly in preclinical or early clinical stage, eribulin approved for advanced BC	Target multiple pathways, overcome some resistance; limited clinical approval, unique mechanisms, but research ongoing; promise for TNBC.	[8]

With the position of more than 70 % of the earth surface area, the marine world is home to a significantly underutilized repository of various bioactive substances with significant pharmacological potential value [9]. Marine sponges are among marine organisms that biosynthesise structurally unique bromotyrosine alkaloids that possess scaffolds donated by tyrosine with halogen substituents [10]. These substances exhibit a wide range of biological effects, including strong cytotoxic, anti-proliferative and anti-metastatic effects against such aggressive malignancies like TNBC [11]. Mechanistically, bromotyrosine alkaloids induce programmed cell-death (apoptosis), cell-cycle stalling and inhibition of oncogenic signalling pathways, such as the PI3K/Akt/mTOR, these effects could provide benefits over existing chemotherapies that are often subject to resistance [12]. Despite the potential of such marine-derived agents as the subject of preclinical research, there is no information about their use in the treatment of TNBC, which is still exploratory [13]. Investigations into these natural products should therefore become a priority because it presents novel framework of pharmacognostic therapy that has been shown to counter the high unmet needs of TNBC [14].

Literature search strategy: A comprehensive literature search was conducted to identify relevant studies related to marine sponge-derived bromotyrosine alkaloids and their anticancer potential, with particular emphasis on TNBC. Scientific databases including PubMed, Scopus, Web of Science, and Google Scholar were searched to collect relevant research articles.

The literature search was performed using combinations of keywords such as “bromotyrosine alkaloids”, “marine sponge-derived alkaloids”, “anticancer activity”, “triple-negative breast cancer”, “TNBC”, “apoptosis”, “cell cycle arrest”, “migration and invasion”, and “molecular signaling pathways”. Articles published from 2020 to 2025 were considered for inclusion.

Studies were selected based on their relevance to the structural characteristics, biological activities, anticancer mechanisms, and TNBC-related experimental findings of bromotyrosine alkaloids. Research articles, review articles, and experimental studies reporting cytotoxicity, apoptosis induction, cell-cycle regulation, signaling pathway modulation, and anti-metastatic effects were included.

Studies unrelated to bromotyrosine alkaloids, non-cancer applications, duplicate publications, and articles lacking sufficient experimental evidence were excluded. The selected literature was critically analyzed to summarize the current understanding of bromotyrosine alkaloids as potential therapeutic candidates against TNBC.

2. Marine Pharmacognosy and Chemical Diversity

2.1 Overview of Marine Pharmacognosy in Cancer

Marine pharmacognosy is a structured investigation into the organized isolation, characterisation, and biological testing of bioactive natural products derived through marine invertebrates, algae, sponges and bacteria-animal and plant life forms subjected to special ecological pressures and hence produce metabolites bearing unique biological activity [15]. Especially in more recent decades, the field has drawn significant attention in oncology in terms of establishing compounds capable of inhibiting cancer-cell proliferation through non-equivalent mechanistic pathways to terrestrial analogues, a result driven by marine natural products [16]. The notability of such secondary metabolites to antitumour activity against breast, lung, kidney, and melanoma cell lines has been attributed to the causing of apoptosis, cell-cycle arrest, and angiogenesis and prevention of metastasis [17]. Particularly, sponge derived compounds have shown promise to overcome mechanisms of resistance in TNBC by antagonizing key signalling pathways [8]. Such evidence gives marine pharmacognosy the advantage of being at the forefront in anticancer drug discovery as a source of structural novelty and therapeutically useful agents is highly available [18].

2.2 Discovery of Bromotyrosine Alkaloids: Marine Sponge Sources, Taxonomy, and Chemical Classification

The bromotyrosine alkaloids form a chemically unique group of heterocyclic natural products almost exclusively derived from invertebrate sponges of the order, Verongida, but mostly those sponges growing in tropical and subtropical oceans where bromine is abundant [1,19]. This group are scattered through the genera Aplysina, Psammaplysilla, Ianthella and these species synthesize congeners, purealidins, bastadins and psammaplins [7]. A total of more than 800 compounds has been detected and the alkaloids fall into categories of mono-1-hydroxy, di-1-hydroxy and n-oxide derivatives, with important subgroups being the Spiro-isooxazoline forms and dimeric bastadins [20].

2.3 Novel Biotechnological Extraction and Structure Elucidation Methods

Recent developments in biotechnology have changed the manner of marine natural products extraction and characterization to even easier obstacles to investigation because of their rarity and chemical complexity [21]. Extremely selective and efficient extraction/isolation of labile metabolites, and considerably high retention of bioactivity compared to the traditional solvent methods, can be achieved using superior methodologies such as supercritical fluid and microwave-assisted extractions [22]. A liquid-liquid extraction is performed at first, and then it is followed by a more sophisticated chromatographic purification [high pressure liquid chromatography (HPLC), thin layer chromatography (TLC) and column chromatography] that results in a highly specific and clean separation of

bioactive components [23]. In order to offer a priority of pharmacological relevance in the situation of isolation, bioassay- guided fractionation is coupled to cytotoxicity and antioxidant screens [24]. It is now possible to use high-resolution 2-dimensional nuclear magnetic resonance (2D NMR), mass spectroscopy (MS) and crystallography to tell conclusively about more complicated marine structures and computational equipment, including cheminformatics and molecular docking are now enabling quick lead optimization and increased mechanistic insight [25].

2.4 Benefits & Difficulties of Isolating Marine Natural Products

Mediterranean natural materials are excellent sources of chemical variety and lead structure substrates that have strong cancer fighting properties, particularly when it comes to tumours that are resistant to several drugs [26]. However, their low natural abundance, the biosafety implications of large-scale extraction, and the technical challenge of isolation or synthesis of structurally complex molecules impairs translation into the clinical realm [27]. Such constraints place a challenge on reproducibility, scalability, and sustainability, making drug development using marine sources quite techno and environmental intensive [28]. This means that marine pharmacophores still have the therapeutic potential in the field of oncology but it remains dependent upon further development of total synthesis, biotechnological synthesis and the protection of marine ecologies [29].

3. Landscape of Bromotyrosine Alkaloids: What Makes Them Unique

3.1 Structural Classification of Bromotyrosine Alkaloids and Influence of Functional Groups on Bioactivity

Bromotyrosine alkaloids are a group of natural products that are mostly derived by marine sponges and that contain brominated phenolic groups based on L-tyrosine, and which have either cyclic or acyclic ring systems further diversified by an array of side-chain substituents [19]. The aromatic ring in the compounds is usually supplemented with bromine atoms, which contributes to the lipophilicity of the compounds, heightens molecular recognition, and increases affinity with the receptors [30]. In this series, the constituents can be monomers with various side chains, or symmetrical and asymmetrical dimers such as with the bastadins, and so provide a large pharmacological diversity [31]. Structural motifs such as phenolic hydroxyl groups, electrophilic bromine atoms and rigid spiro conformations are also used to facilitate selective protein binding, the basis of cytotoxicity, enzyme inhibition, and signaling pathway modulation [32]. Further, halogen substitution contributes to increased metabolic stability and pharmacokinetic half-lives, and thus, it supports the selective activity of the compounds to the resistant cancer phenotypes [33].

Based on their characteristic chemical scaffolds, bromotyrosine alkaloids can be broadly classified into several structural classes, including spirocyclohexadienylisoxazoline-type alkaloids, psammaplysin-type alkaloids, bastadin-type alkaloids, and other bromotyrosine-derived metabolites. Spirocyclohexadienylisoxazoline alkaloids represent one of the most recognized classes and are characterized by a distinctive spirocyclic ring system formed through cyclization of brominated tyrosine-derived units. Psammaplysin-type alkaloids are mainly distinguished by their dimeric structures containing bromotyrosine-derived units linked through ether or amide connections, which contribute to their diverse biological activities. Bastadin-type alkaloids are symmetrical or asymmetrical dimers containing brominated aromatic moieties and have demonstrated significant pharmacological properties, including cytotoxic and enzyme-modulatory effects. Other bromotyrosine alkaloids possess diverse side-chain modifications and functional groups, resulting in variation in molecular interactions and biological responses.

The structural diversity of bromotyrosine alkaloids is closely associated with their pharmacological activities, as specific functional groups such as bromine substitutions, phenolic hydroxyl groups, and spirocyclic frameworks influence molecular binding, antioxidant potential, enzyme inhibition, and anticancer effects. A representative classification and chemical structures of major bromotyrosine alkaloid classes are presented in Figure 1 to provide a better understanding of their structural features and relationship with bioactivity.

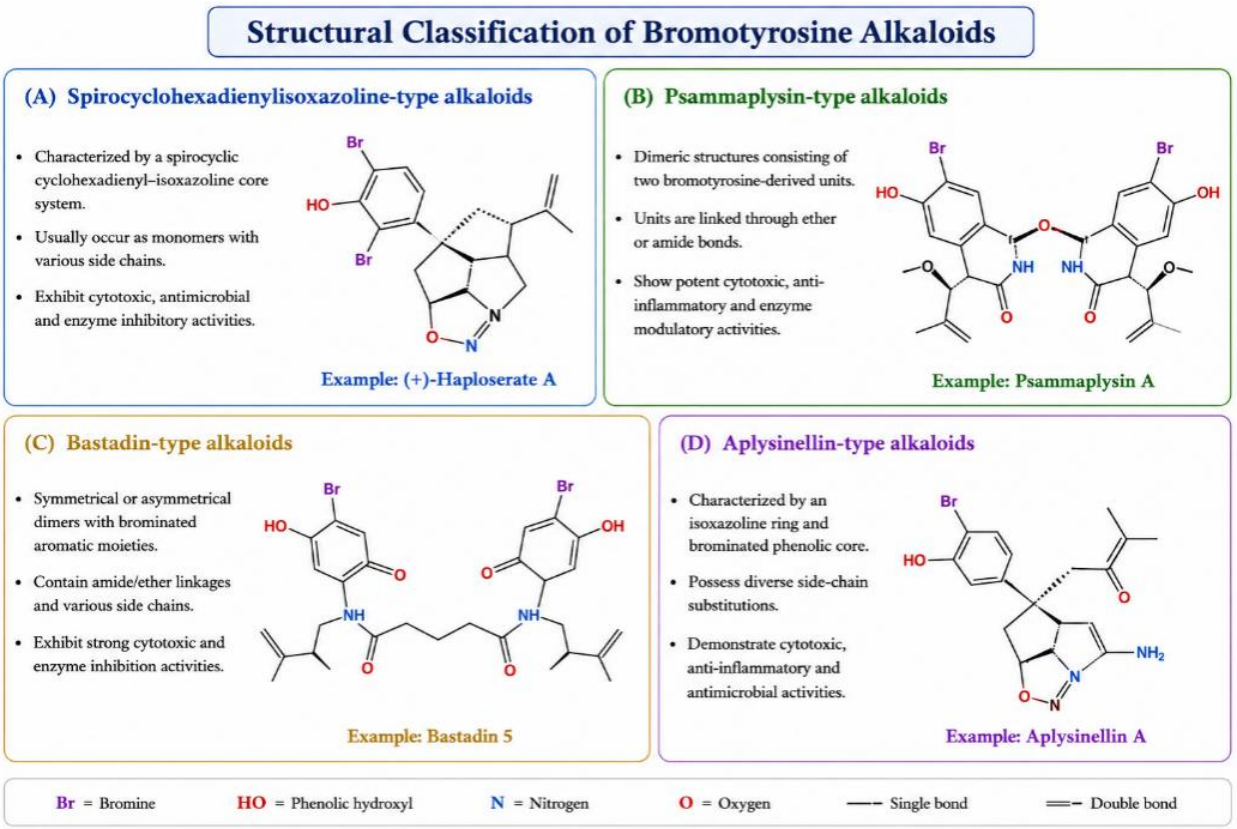


Figure 1. Representative chemical structures of major classes of bromotryrosine alkaloids showing their characteristic scaffolds and key functional groups associated with bioactivity.

3.2 Previously Reported Bioactivities: A Comprehensive Survey

Bromotyrosine alkaloids comprise a structurally diverse group of natural products that have reported bioactivities, including cytotoxicity toward a spectrum of cancerous cell types to anti-fungal, antiviral, antioxidant, and immunomodulatory activities [34]. These molecules act on enzymes associated with cancer, and which pathways entail the disease, mainly histone deacetylase and DNA methyltransferase, and hence, reveal epigenetic drug potential [35]. It is interesting to note here that bromotyrosine alkaloids have been extensively explored in their anticancer potential but are relatively insufficient in their efficacy against a given type of breast cancer, which is an unachieved future research goal [36]. However, despite their diverse biological activities, most reported findings are based on preliminary *in vitro* studies, and limited information is available regarding pharmacokinetic behavior, toxicity profiles, and clinical translation, particularly in TNBC models.

3.3 Uniqueness in Targeting Cancer Types-Evidence of Underexploration in Breast/TNBC

Alkaloids of bromotyrosine are a promising, novel category of anticancer therapies that have proven to be effective in a variety of malignancies, but their use in the case of breast cancer-specifically TNBC studies have been poorly explored so far [37]. The loss of oestrogen, progesterone and HER2 receptors in TNBC makes it resistant to the conventional therapeutic modes, thus making it need a new approach in the clinical arena [38]. Preclinical observations have supported that certain bromotyrosine derivatives have the potential of causing apoptosis, the destabilization of tubulin, and disruption of DNA production in breast cancer cell lines [39]. The most notably is Psammaplin A which has dual inhibitory action on major enzymes of epigenetics [40]. Despite this mechanistic evidence there is limited systematic screening against TNBC cell lines, and the emerging structure-activity relationships are poorly characterized [41]. Considering the aggressive nature, and poor prognosis of TNBC, it is an urgent pharmacological priority to capitalize on the pharmacognostic potential of the bromotyrosine alkaloids, particularly, the multifunctional spectrum of their action, with interest in antioxidant activity, epigenetics, and anti-angiogenesis [42].

Although bromotyrosine alkaloids have demonstrated broad anticancer activities across different malignancies, their specific evaluation in TNBC remains comparatively limited. TNBC represents a clinically aggressive breast cancer subtype characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, resulting in limited targeted therapeutic options. Experimental studies using TNBC-associated cell lines, particularly MDA-MB-231, have reported that bromotyrosine alkaloids can influence key cancer-related processes including apoptosis induction, cell-cycle arrest, inhibition of proliferation, and modulation of survival signaling pathways. However, direct comparative investigations between TNBC and hormone receptor-positive breast cancer models such as MCF-7 remain insufficient. Therefore, further TNBC-focused pharmacological studies, including evaluation of

subtype-specific responses, molecular targets, and translational relevance, are required to establish the therapeutic potential of bromotyrosine alkaloids.

3.4 Theoretical and Computational Predictions for Anti-TNBC Efficacy

Using in silico analysis, it has been determined that bromotyrosine alkaloids have a strong predicted binding affinity to major TNBC targets, including checkpoint kinases (Chk1/Chk2), anti-apoptotic proteins [B cell lymphoma-2 (Bcl-2), myeloid cell leukemia-1 (Mcl-1)] and PI3K/Akt/mTOR signaling kinases [43]. The halogenated side chains increase the selectivity and the overall stability of the ligand-target interactions through interactions by halogen bonding and hydrophobic effects, as supported by molecular dynamics simulations showing long-range target-ligand interactions [44]. The comparison of Bromotyrosine alkaloids and anti-cancer properties; novelty score shown in Table 2.

Table 2. Bromotyrosine alkaloids and anti-cancer properties; novelty score.

Bromotyrosine Alkaloid	Sponge Source / Origin	Reported Anti-Cancer Properties	Cancer Type(s) Tested (Cell Line)	Novelty Score*	Ref.
Clavatadine C	*Suberea clavata* (marine sponge)	Moderate cytotoxicity; selective antiproliferative effects	Breast cancer (MCF-7, MDA-MB-231); Lung cancer (A549)	4 (High)	[19]
Psammaplin A	Various sponges of order Verongida	Dual HDAC and DNMT inhibition; epigenetic modulation	Breast cancer (TNBC models)	5 (High)	[45]
Bastadins	*Ianthella* genus	Cytotoxicity; calcium/calmodulin kinase inhibition	Leukemia; Breast cancer	3 (Moderate-High)	[46]
Aerophobin-2	*Aplysina* genus	Cytotoxicity; apoptosis induction	Leukemia; Breast cancer; Lung cancer; Epidermoid carcinoma	3 (Moderate)	[47]
FBA-TPQ (synthetic analog)	Synthetic derivative inspired by marine alkaloids	Apoptosis induction in breast cancer cell lines	Breast cancer (MDA-MB-231, MCF-7)	3 (Moderate-High)	[48]
Spirocyclic Clavatadine analogs	*Suberea clavata* derivatives	Potent cytotoxicity	Melanoma (A-375)	4 (High)	[49]
3-Bromofascaplysin	*Thorectandra* sp. sponge	Inhibition of breast cancer cell proliferation	Breast cancer (MCF-7, T-47D, MDA-MB-231)	3 (Moderate)	[50]
Psammaplysene D	Various marine sponges	Strong cytotoxicity (IC_{50} ~0.7 μM)	Carcinoma (KB cell line)	3 (Moderate)	[51]

Absorption, distribution, metabolism, elimination and toxicity (ADMET) profiling predicts good pharmacokinetic parameters such as decent membrane permeability, oral bioavailability, with some members having low solubility that might necessitate prodrug modifications [52]. Structure-activity relationship modeling predicts that the spiro-isooxazoline analogues achieve better target affinity and metabolic stability as compared with the corresponding linear analogues [53]. Taken together, these computational results can offer a strong scientific justification to *in vitro* and in vivo studies thus bridging translational gap between chemical innovation and potential TNBC therapies provided that the chemical candidates so identified through pharmacological studies justify clinical validation [54].

4. Pharmacological Activities against TNBC

4.1 *In Vitro* Cytotoxicity Profiles: Summary and Recent Findings in TNBC Cell Lines

Marine sponge-derived bromotyrosine alkaloids have potent cytotoxic effects on TNBC cell lines, which demonstrate potential therapeutic value [55]. These compounds also alter pathways of major interest in signaling. *Monanchora viridin* (Crambescidin 800) induces cell cycle arrest in TNBC cells at the G2/M phase and modulates multiple proliferative and survival-associated pathways, including Akt/mTOR, nuclear factor-κB (NF-κB), and mitogen-activated protein kinase (MAPK) signaling. Although reduced expression of cyclin D1 and CDK4/6 has been reported, these regulators are primarily involved in G1/S phase transition and may reflect an overall suppression of proliferative signaling. The observed G2/M arrest is more closely associated with modulation of G2/M checkpoint regulators, including cyclin B1, CDK1, p21, and p53 pathways. In the same line of thought, *Stylissa carteri* extracts also showed dose-dependent cytotoxicity and cell growth inhibitory properties on apoptotic modulation and blocking of metastasis enhancement of chemotherapeutic activity [56]. The mechanistic studies show that bromotyrosine alkaloids induce apoptosis through the activation of caspase, the cleavage of PARP, the formation of reactive oxygen species, the mitochondrial dysfunction along with the reduction in the resistance to various stress stimuli. Together, these data argue the further development of bromotyrosine alkaloids as potent cytotoxic agents against the aggressive TNBC phenotype [57].

4.2 Selectivity and Toxicity: Comparison with Non-Cancerous Breast Epithelial Cells

Cancer selectivity is an essential pharmacological aspect, and preclinical studies showed a significant tumor cell specificity cytotoxicity by Aplyzanzine B and anomoian B [58]. This is supported by evidence of retained mitochondrial integrity and minimal expression of apoptotic-factors in these healthy cells up to the same doses. These similar trends are acquired using the derivatives of the FBA-TPQ which exhibit selectivity to the TNBC cells relative to the normal mammary cells [59]. This selectivity could also be further justified by differential expression and signaling cascades of p53 so that malignant cells become more vulnerable to cell-cycle abrogation and apoptosis [60].

4.3 Pharmacologic Evidence for Apoptosis, Cell Cycle, and Migration/Invasion Assays

This is an extended pharmacology: the bromotyrosine alkaloids are demonstrated to be powerful anti-neoplastic agents in TNBC [61]. Further, they are also known to display cytostatic activity through cell-cycle arrest, often in the G1 or G2/M phases as shown by Crambescidin 800, which inhibits cyclin D1, CDK4, and CDK6 and altered other key signaling pathways Collectively, these data demonstrate the multipronged anticancer activity of bromotyrosine alkaloids, which can act by triggering apoptosis, block proliferation, and prevent metastasis, having the potential to target all hallmarks of the aggressive TNBC phenotype [62]. The apoptotic effects of bromotyrosine alkaloids have been supported by several molecular and cellular investigations, including increased caspase activation, poly(ADP-ribose) polymerase (PARP) cleavage, regulation of pro- and anti-apoptotic proteins such as Bax and Bcl-2, and induction of oxidative stress through reactive oxygen species (ROS) generation. These findings indicate that bromotyrosine alkaloids can activate programmed cell death pathways in TNBC cells. In addition to apoptosis induction, cell cycle analysis using flow cytometry has demonstrated that bromotyrosine alkaloids can interfere with cell-cycle progression by inducing phase-specific arrest. Although some studies have reported alterations in cyclin D1 and CDK4/6 expression, these proteins are mainly associated with G1/S phase regulation, whereas G2/M arrest involves additional checkpoint regulators such as cyclin B1, CDK1, p21, and p53 pathways. Furthermore, the anti-metastatic potential of bromotyrosine alkaloids has been evaluated through migration and invasion assays, including wound-healing and transwell-based approaches. These compounds may suppress metastatic behavior by regulating epithelial–mesenchymal transition (EMT)-related markers and reducing the expression/activity of matrix metalloproteinases (MMP-2 and MMP-9), which are essential for tumor cell migration and invasion.

4.4 Synergistic Effects with Standard Chemotherapeutic Agents

Marine sponge-derived, Bromotyrosine alkaloid bioactive agents are a structurally unique group of bioactive agents that have shown strong anticancer profile against TNBC [63]. However, definitions of key steps in interpreting *in vitro* results and applying them in vivo, clarity into structure-activity, and scaling-up of durable, sustainable production, are gaps that require attention. One should collaborate in various fields to bring about the effectiveness of TNBC treatment by using these marine-derived compounds [64].

4.5 Overcoming Multi-Drug Resistance in TNBC

Bromotyrosine alkaloids have the propensity to allow multidrug resistance (MDR) in the TNBC through the regulation of pathways that express drug excretion, apoptosis resistance, and cell detoxification as depicted in Figure 2 [65]. The compounds have the potential to maintain accumulation of anticancer drugs within the cell since their unique scaffolds are not subject to efflux. Despite the fact that conclusive evidence to TNBC-reversal of MDR is scarce, there exist sufficient mechanistic knowledge to continue the exploration of bromotyrosine alkaloids as supportive agents that would concurrently augment the outcome of chemotherapy in resistant TNBC subtypes [66]. Figure 2 provides a schematic overview of the proposed mechanisms through which bromotyrosine alkaloids may influence multidrug resistance and anticancer responses in TNBC. The Figure 2 highlights the involvement of major resistance-associated processes, including drug efflux regulation, apoptotic resistance, cellular detoxification mechanisms, and modulation of survival signaling pathways. By targeting these interconnected pathways, bromotyrosine alkaloids may enhance intracellular drug accumulation, promote apoptosis, and improve the sensitivity of resistant TNBC cells to chemotherapy. However, further experimental validation is required to establish their direct role in reversing MDR and improving therapeutic outcomes.

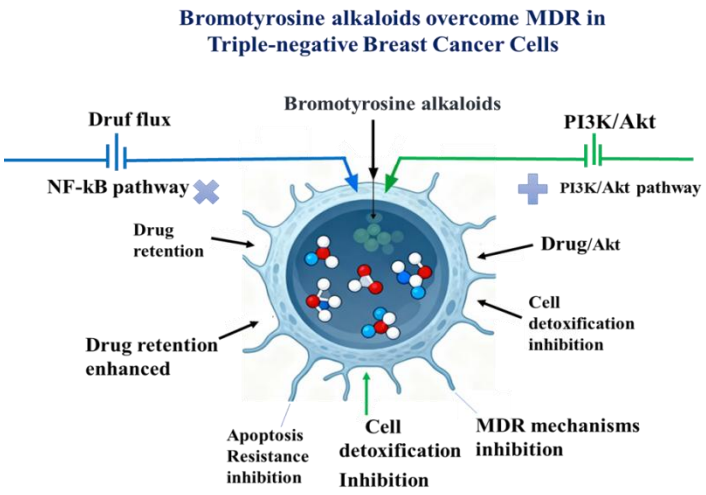


Figure 2. Schematic representation of the inhibitory effects and molecular pathways targeted by marine sponge-derived bromotyrosine alkaloids in TNBC cells: highlighting their role in apoptosis induction, cell-cycle regulation, modulation of survival signaling pathways, and inhibition of migration/invasion and multidrug resistance-associated mechanisms.

5. Mechanisms of Action and Molecular Targets

5.1 High-Level Overview of Known and Predicted Anti-Cancer Mechanisms

Isolated bromotyrosine alkaloids of marine sponges exemplify a unique anticancer efficacy by the multifactorial modulation of processes essential to the survival, proliferation, and metastatic capabilities of cancer cells [67]. Moreover, bromotyrosine alkaloids interfere with cell-cycle checkpoints at the G1 and/or G2/M stages, which unsetts the proliferation of the tumor. These agents also have the properties of inhibition of angiogenesis, alteration of signaling pathways, e.g., Nf-κB and PI3K/Akt/mTOR axis, induction of autophagy, and causing DNA damage, which altogether lead to increased cytotoxic efficacy [68]. Computational simulations support a high binding affinity to oncogenic proteins, and explains the multifactorial anticancer property of the bromotyrosine alkaloids. Cumulatively these mechanisms depict a broad-spectrum anti-tumor ability against aggressive cancer subtypes, such as TNBC, with less resistance and a diminished capacity to metastasis as shown in Figure 3 [69].

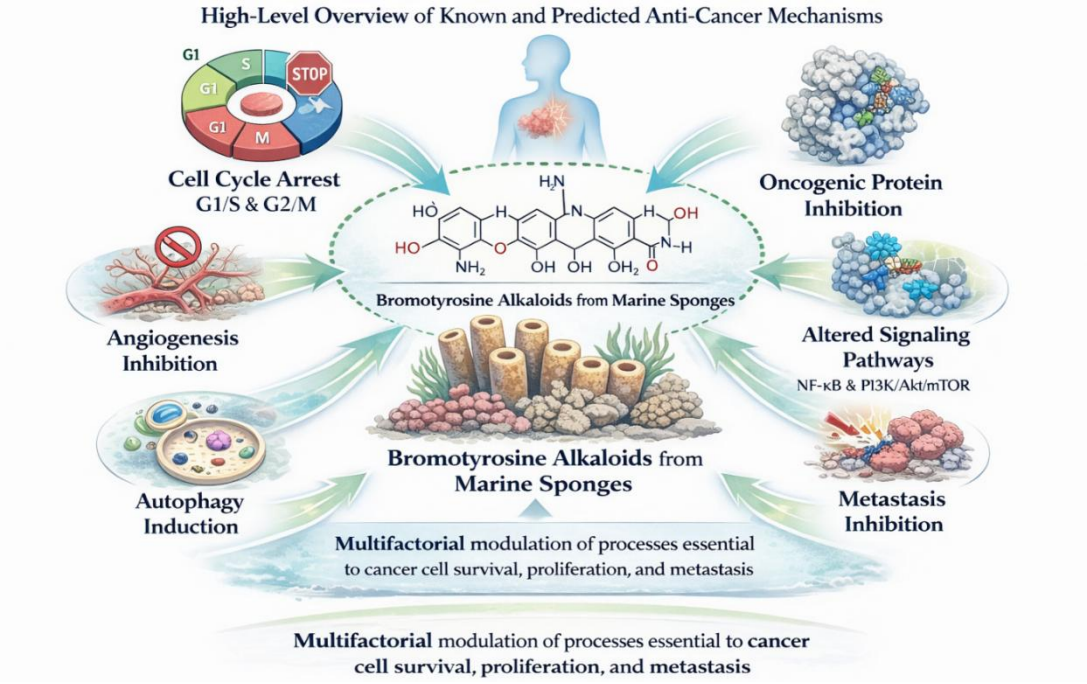


Figure 3. Modes of action of marine sponge–derived bromotyrosine alkaloids in TNBC.

5.2 Modulation of Oncogenic and Tumor Suppressor Pathways

Bromotyrosine alkaloids exert significant effect on oncogenic and tumor-suppressor mechanisms of cancer cells. Meanwhile when they inhibit the Nf-κB pathway in which anti-apoptotic/inflammatory proteins are decreased, they increase the vulnerability of the cancer cells to death [70]. Moreover, they prevent PI3K/Akt/mTOR pathway and thus

impair cell growth and cell survival and promote autophagy and apoptosis using fascaplysin-4-chloro. In addition, bromotyrosine alkaloids modify the MAPK and STAT3 pathways; the latter disrupts the proliferation/apoptosis balance. It has been demonstrated that these alkaloids have a non-selective effect on disrupting the homeostasis of cancer cells by integrating oncogenes blockage and tumor suppressors activation, which further justifies their great therapeutic potential [71].

5.3 Epigenetic Modulation, Autophagy, and Induction of DNA Damage

Bromotyrosine alkaloids generally regulate cancer progression by various types of epigenetic mechanisms including the inhibition of histone deacetylases (HDACs) and DNA methyltransferases (DNMTs). One more example, which is considered to be a mechanism of action, is Psammaplin A, which restores the silence of tumor gene transcription in TNBC, thereby triggering apoptosis and enhancing responsiveness to chemotherapy of the cancer [72]. In addition, it is demonstrated that some members of this family are also using autophagy, an intracellular catabolic process. Such compounds as calothrixin A stabilizing the enzyme-DNA complex which forms discontinuities in both strands or double-strand breaks directly changes the activity of DNA topoisomerase I, which is also stimulated by reactive oxygen species [73]. The DNA-damage associated stress also makes TNBC cells sensitive to chemotherapeutic agents, which holds potential synergistic treatment. The ability to interact with epigenetic reprogramming and autophagy induction, as well as the administration of pathways of DNA-damage suggests that this family of compounds have broad-spectrum anticarcinogenic properties, collectively [74].

5.4 Targeting of Cancer Stem Cells and Microenvironment Modulation

The relatively recent studies suggest that bromotyrosine alkaloids have a significant potential to attack cancer stem cells (CSCs) the cell population triggering the emergence of tumors, their metastasizing, and chemotherapy resistance in aggressive TNBC. These can mediate multiple critical signalling pathways such as Nf-κB and PI3K/Akt, shutting down CSC self-renewal and survival, resulting in a decreased number of CSCs [75]. Moreover, bromotyrosine alkaloids demonstrate a response in the tumour microenvironment by inhibiting vascular endothelial growth factor (VEGF)-induced angiogenesis, which is especially prominent in fascaplysin analogues, thereby retarding the development of the tumour and metastatic proliferation. The disruption of CSCs and their cordial conditions by these alkaloids makes them a complex treatment therapy with the capacity to treat TNBC with improved results [76].

5.5 Omics-Based Elucidation: Transcriptomic and Proteomic Shifts

This is because with the use of omics, an overarching picture of the concept of antitumor activity of bromotyrosine alkaloids can be given in regard to cancer cells. Transcriptomics also reveal the prevention of the gene connected with the cell-cycle progression Bcl-2 family members and the matrix metalloproteinases [77]. These data are subsequently complemented by additional proteomic data that claim decreased phosphorylation of oncogenic kinases (Akt, mTOR, STAT3), decreased EMT indicates, and subsequent inhibition of movement and intrusion of TNBC models. Concurrently, the pro-apoptotic proteins and DNA-damage markers increase, which assure activation of the apoptosis and genotoxic stress [78]. On top of this, the synthesis of the omics data indicates on the metabolic reprogramming that decrease the tumor fitness. These complicated molecular changes have defined the pharmacodynamics of bromotyrosine alkaloid and can lead to the discovery of biomarkers to enable targeted monitoring in the process of pharmaceutical treatment [79].

5.6 Pharmacokinetic and Structural Biology Insights

Close X-ray based analysis of bromotyrosine alkaloids and use of pharmacokinetic and structural techniques demonstrated excellent bioavailability and metabolic stability properties [80]. Interaction with TNBC-related targets, HDACs, and kinases have been structurally elucidated with a combination of NMR and X-ray crystallography as having been stabilized by halogen bonds, hydrogen bonds, and hydrophobic interactions [81]. Continued pharmacokinetic and structural studies are essential to the further development of clinically viable candidates based on these marine alkaloids as future treatment of TNBC [82]. The comparison of molecular targets and pathways in TNBC shown in Table 3.

The Modes of Action of Brominated Bromotyrosine Alkaloids of Marine Sponge against TNBC cells. The compounds cause apoptosis, DNA damage, caspase activation; they have anti-proliferative (e.g., MAPK/PI3K/Akt inhibition) activity and anti-metastatic (e.g., EMT inhibition) functions as well. Importantly, they also exhibit anti-angiogenic effects in terms of VEGF decreasing, addressing the tumor growth and expansion.

Table 3. Molecular targets and pathways in TNBC.

Molecular Target / Pathway	Description of Modulation by Bromotyrosine Alkaloids	Role in TNBC and Therapeutic Implication	Ref.
p53 Tumor Suppressor	Activation and stabilization leading to enhanced apoptosis and cell cycle arrest (e.g., FBA-TPQ)	Critical for DNA damage response and tumor suppression; often dysfunctional in TNBC	[83]
Nf-κB Pathway	Inhibition of Nf-κB activation reduces anti-apoptotic gene expression and inflammatory signaling	Key regulator of cancer cell survival, inflammation, and chemo-resistance in TNBC	[84]
PI3K/Akt/mTOR Signaling	Suppression of Akt and mTOR phosphorylation inhibits proliferation, induces autophagy and apoptosis	Frequently hyperactivated in TNBC, driving growth, survival, and therapy resistance	[85]
HDAC/DNMT Epigenetic Modifiers	Dual enzymatic inhibition (e.g., psammaplin A) reverses epigenetic silencing of tumor suppressor genes	Epigenetic dysregulation contributes to TNBC progression and drug resistance	[86]
Caspase Cascade	Activation of caspase-3 and caspase-9 pathways mediates mitochondrial apoptosis	Executes programmed cell death critical for eliminating cancer cells	[87]
Reactive Oxygen Species (ROS)	Induction of oxidative stress disrupts mitochondrial function and triggers apoptosis	Elevated ROS can selectively kill cancer cells by tipping redox balance	[88]
Cell Cycle Regulators (Cyclins/CDKs)	Downregulation of cyclin D1, CDK4/6 causing G1 or G2/M arrest	Dysregulated cell cycle progression underpins uncontrolled TNBC proliferation	[89]
Matrix Metalloproteinases (MMPs)	Inhibition of MMP expression decreases tumor cell invasion and metastasis	MMPs facilitate extracellular matrix degradation, promoting metastasis in TNBC	[90]

6. Pharmacognostic and Analytical Advances

6.1 Standardization and Quality Assurance of Marine-Derived Compound Extracts

Practical application of marine-derived bromotyrosine alkaloids to make therapeutic use would require strict standardization as well as extensive quality control mechanisms to address the variation offered by geographical origin, seasons, and environmental factors [91,92]. The first one implies the accurate identification of a target species with the use of taxonomic and molecular-based techniques. Thereafter, extraction guidelines such as the use of standardized reagents, changes in pH and strict temperature control shall be used to achieve a consistent bioactive alkaloid profile [93]. These methods include chemical fingerprinting methods (HPLC, mass spectrometry and NMR) which help identify and quantify the marker compounds correctly. Combining these, they may lead to the enhancement of inter-study reliability and assist in the safe and effective transfer of medicine derived in the marine environment to the clinical environment [94].

A systematic workflow is required for the discovery and development of marine-derived bioactive compounds to ensure reproducibility and therapeutic reliability. As illustrated in Figure 4, the overall pipeline includes marine sample collection and species authentication, extraction and isolation of bioactive compounds, chemical characterization using analytical techniques, biological activity screening, mechanistic evaluation, and quality control standardization. This integrated approach helps minimize variability associated with environmental factors and ensures consistent evaluation of marine-derived bromotyrosine alkaloids for potential clinical applications.

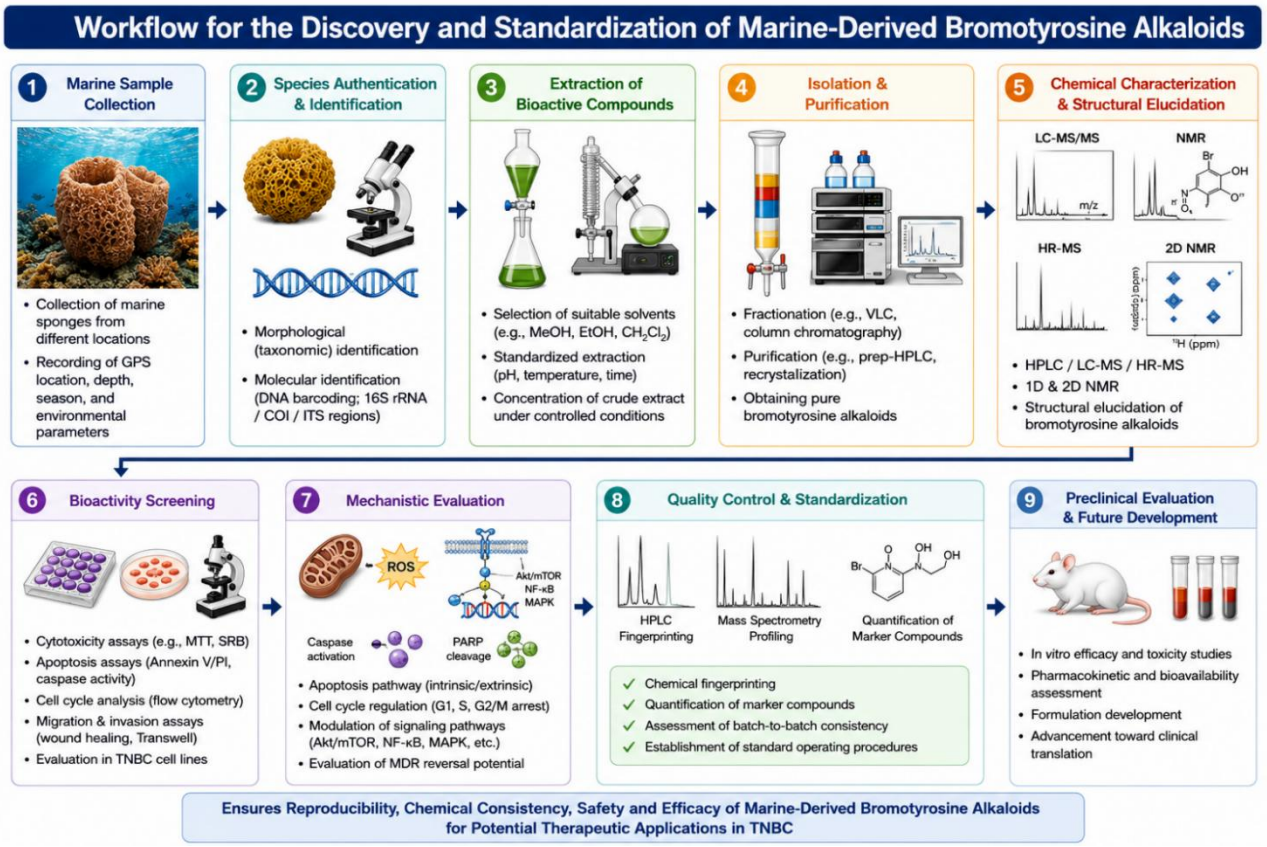


Figure 4. Workflow for the discovery, characterization, bioactivity evaluation, and standardization of marine sponge-derived bromotyrosine alkaloids.

6.2 Spectroscopic & Chromatographic Methods for Identifying Compounds

Bromotyrosine alkaloids are structurally heterogenous and relatively scarce, thus making research of bromotyrosine alkaloids in complicated marine preparations tedious. The recent advances in the chromatography and spectrometric methods, however, revolutionized identification and structural characterization [95]. Volatile compounds can be analyzed using gas chromatography with complementary methods and mass and high-resolution fragmentation analysis of mass, as well as electrospray ionization and matrix-assisted laser desorption/ionization, can be accurately measured [96]. Issues of incorporation of such spectral data justifies bromination schemes and these functional groups that incriminate bona fide these alkaloids directly as being biologically active. Bioassay-driven separation and structure 41 - activity relationship studies: Structure activity relationships Discovery of new compounds, as well as known analogs, has been hastened with the advent of ultrahigh-performance liquid chromatography, along with orbitrap-based mass spectrometry, ensuring marine pharmacognosy [97].

6.3 Advances in Bioassay-Guided Isolation and Structural Validation

Bioassay-directed purification is an imperative system of isolating the bioactive compounds of complicated marine sponge extracts. The first step of the protocol is preliminary extraction and a two-solvent partitioning which is followed by a systematic fractionation using liquid-liquid extraction, column chromatography, and HPLC [98]. Strict evaluation of fractions will also be done at each step by quantifying cytotoxicity, apoptosis induction and other pharmacological potentials in TNBC and other cell lines in a triage fashion in order to determine the most productive fractions. Recent advances on automated micro-fractionation and high-throughput screening, in addition to integrative data analysis, have made this workflow simpler and enabled the uncovering of rare bioactive compounds by itself. The remedies of the future will involve the methods of crystallography and of computer modeling which will augment the molecular characterization and harness the pharmacological possibility of these sea-derived alkaloids [99].

6.4 Chemo-Biodiversity Conservation and Sustainable Sourcing

The balance between the accelerated pace of the research and environmental protection requires systematic bromotyrosine alkaloids harvesting of marine origin. Chronic overexploitation of the sponges causes them to face extreme danger of dead biodiversity and habitat destruction thereby forcing the application of conservation based harvesting approaches-rotational management, aquaculture and mariculture, which conserve the wild stocks [100]. The more modern synthetic and semi-synthetic approaches now allow the systematic production and functional variability of bromotyrosine scaffold-devoid of limitations of supply and expansion of pharmacological effects [101]. Responsible

bioprospecting has focused on ethical sourcing procedures, i.e., the ability to identify and collect specimens, the registration of data, and traceability, which have been supported by partnerships involving marine biologists, marine chemists and regulatory authorities. These combined efforts collectively are maintaining marine biodiversity and also using it to identify and derive newer anticancer pharmacotherapeutics [102].

7. Preclinical and Emerging Clinical Evidence

7.1 Animal Models: Efficacy and Safety Studies of Bromotyrosine Alkaloids

Preclinical studies using immunocompromised mice engrafted with TNBC cell lines, including MDA-MB-231, have already shown that bromotyrosine alkaloids and their artificially created counterparts led to dose-dependent tumor growth suppression with little or no observable toxicity in the body [103]. Besides, these alkaloids suppressed tumor-related inflammation and angiogenesis and regulated immune responses in immunocompetent models. Bromotyrosine alkaloids also increased tumor regression and reduced chemotherapy cytotoxicity. Notwithstanding limitations inherent in their translation to human TNBC, given their heterogeneity and complexity, the preclinical evidence as a whole supports the potential of bromotyrosine alkaloids as anticancer agents that merit clinical testing [104].

7.2 Formulation Strategies: Liposomal, Nanoparticle, and Conjugate Technologies

Marine bromotyrosine alkaloids hold potential as an effective therapeutic targets against TNBC, but due to minimal bioavailability and insufficient tumor-specific delivery, their clinical translation is limited to date [105]. The active compounds are shielded by liposomal encapsulation to prevent the degradation of actives and allow slow release by the enhanced permeability and retention (EPR) effect common in neoplastic tissues. Instead, polymer nanoparticles, often surface-engineered to carry targeting ligands, as folate or antibodies prime TNBC cell uptake and limit off-target deposition [106]. The integration of stimuli-responsivity further optimizes the selectivity in that the release of drugs is set in pathophysiological microenvironment in TNBC. Though mainly limited to preclinical research, these emerging delivery routes have immense potential to boost future clinical trials with respect to therapeutic efficacy and safety [107].

7.3 Toxicology and ADMET Profiles in Preclinical Settings

It has been found that the bromotyrosine alkaloids are non-toxicologically profiled and present with favourable ADMET properties. Low *in vitro* cytotoxicity in normal human cell lines and adequate tolerability with rodents indicate that they have no major effects on organs in vivo at therapeutic doses. The pathway of metabolism occurs through cytochrome p450 enzymes in a manner whereby the metabolites are active or cleansed quickly [108]. There is limited aqueous solubility, but the favourable routes of administration allow adequate bioavailability and renal excretion eliminates the accumulation. Currently, chronic and reproductive toxicology studies are needed to be conducted continuously to assess risk fully even pre-clinically [109].

7.4 Prospects for First-in-Human Studies

Bromotyrosine alkaloids are low risk in the area of mutagenicity, genotoxicity, cardiotoxicity, and neurotoxicity, according to both in silico and in vivo ADMET modeling analyses. Safety assessment is not to be underestimated before the customer goes into clinical trials and that requires conducted chronic and reproductive toxicology [110]. By applying biomarkers to stratify patient cohorts by disrupting pathways of critical importance, e.g. p53 and Nf-κB, more effective targeted therapies and expedited clinical translation can be generated. In order to achieve these translational opportunities in the treatment of TNBC, this multidisciplinary approach on the gaps between preclinical and clinical pharmacology needs to be continued [111].

8. Challenges, Opportunities, and Future Roadmap

The Bromotyrosine alkaloids would have a significant future as a treatment option of TNBC, especially when patient stratification is informed with biomarker discovery of the key molecular controllers including p53 and Nf-κB. Mass manufacturing, on the other hand, requires a high-level of quality control and toxicological testing and conformity to global regulations, such as Nagoya Protocol. The issue of intellectual-property in the case of natural products implies the importance of developing artificial analogues and improved methods of extraction. Computational modeling and artificial intelligence should streamline the process of designing drugs and overcome the heterogeneity of TNBC. The availability and scalability will be guaranteed by sustainable biotechnological synthesis methods, including the microbial fermentation. Such regulatory cooperation combined with adaptive clinical trial design will also facilitate translational. The introduction of more formulation improvements to enhance bioavailability will bring BTAs as a central element of next-generation oncology pipelines hence inculcate innovation in marine-based pharmacognostic.

9. Conclusion

Marine bromotyrosine alkaloids are favourable anticancer targets due to the brominated structure of the compound and multifunctional groups which target multiple oncogenic pathways in apoptosis, cell cycle arrest, epigenetics and metastasis suppression. Despite its strong *in vitro* and preclinical stage of development, many obstacles exist, including minimal *in vivo* confirmation, little specific TNBC activity data, lack of structure-activity relationships and issues with scalable and sustainable supply. Recent breakthroughs in genomics, proteomics and computational drug design, combined with intelligent drug delivery devices and systems, including nanoparticles, liposomes, and antibody-drug conjugates, will be needed to produce precision-targeted analogues. A sustainable production (be it through chemical synthesis or through the methods of biotechnological innovation) is pivotal to the clinical use. In order to have the best therapeutic results of bromotyrosine alkaloids, it will involve close liaisons in the different fields such as marine biology, chemistry, oncology, pharmacology, clinical sciences and others to ensure scientific integrity, good ethical sourcing, regulatory approvals and come up with convenient translated schemes toward designing targeted and sustainable therapeutics in management of TNBC.

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Ethics Statement

Not applicable. This study is a review article and did not involve human participants, animals, or primary data collection.

Data Availability Statement

No new data were generated or analyzed in this study. Data sharing is not applicable to this article.

Author Contributions

All authors contributed to the conception, writing, revision, and approval of the final manuscript.

Conflict of Interest

The authors declare that there are no conflicts of interest related to this manuscript.

Generative AI Statement

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