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Proceeding Paper

Bromophenols in Red Algae: Exploring the Chemistry and Uncovering Biological Benefits of These Unknown Compounds †

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Abstract: Bromophenols, which belong to the family of phenolic compounds, are halogenated secondary metabolites characterized by the incorporation of bromine atoms into the phenol ring structure, resulting in unique chemical properties. These compounds, synthesized as secondary metabolites by algae, exhibit different isomeric forms due to bromine substitution at different positions within the phenol ring, showing variability among species. Bromine substitution not only confers specific chemical properties but also plays an important role in the ecological functions of bromophenols by inducing increased lipophilicity, which affects solubility and reactivity, an adaptive response to external conditions. Certain genera of red algae, such as *Gracilaria* and *Rhodomela*, have been identified as important sources of bromophenols. Research on bromophenols involves extraction, commonly using solvents such as methanol or methanol-dichloromethane, and identification and structural elucidation using advanced analytical techniques such as mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy for the precise determination of structure and configuration. Bromophenols display diverse biological activities, highlighting antimicrobial, antidiabetic, antiviral and antioxidant properties, which are closely related to their specific chemical structure. The importance of understanding the chemical group of bromophenols is underlined by their role in chemical defense mechanisms, contributing to potential biotechnological applications and broader contributions to the marine ecosystem. Therefore, this study is aimed to review the chemical characteristics and biological properties of bromophenols in red algae.

Keywords: bromophenols; phenolic compounds; secondary metabolites; red algae

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1. Introduction: Red Algae Bromophenol Overview

Bromophenols (BPs) are common marine secondary metabolites classified as polyphenols and biosynthesized by bromoperoxidases in the presence of laccase, bromide, bromate, and hydrogen peroxide [1,2]. Unlike other phenolic compounds, BPs contain multiple bromine atoms and hydroxyl (-OH) groups at different positions on the aromatic ring, which significantly influences their chemical properties and biological activity. The presence of bromine increases their lipophilicity and modulates their reactivity, often resulting in improved antimicrobial, anticholinergic, antidiabetic, antiviral and antioxidant activities compared to non-brominated phenolics [3]. In addition, their reactivity is influenced by carbonyl groups. Carbonyls facilitate the cleavage of OMe bonds through Lewis acid

catalysis. Effective O-demethylation with reagents such as BBr_3 leads to the formation of biologically active derivatives, making BPs promising candidates in medicinal chemistry for targeted therapeutic applications [4].

BPs are found across all major categories of marine algae [3,5,6]. They were first isolated from the red algae *Neorhodomela larix* (formerly known as *Rhodomela larix*) in 1967 [2,7], and subsequently identified and isolated across all taxonomic groups of macroalgae, especially in the red algae of the Rhodomelaceae family [8,9]. They have also been widely identified in species such as *Dasycladus vermicularis* and *Cladophora socialis* (green algae), *Ascophyllum nodosum* (brown algae), *Bifurcaria bifurcata* (brown algae), *Gracilaria* sp. (red algae), and *Ecklonia cava* (kelp algae) [10]. It has been noted that species harvested during low-tide periods tend to have elevated levels of simple BPs [11].

The biosynthetic pathways responsible for producing natural BPs in marine biota are not yet fully understood; authors suggest that tyrosine could be the precursor [12]. At present, there is insufficient research to provide a complete elucidation of the molecular genetic mechanisms underlying their biosynthesis. Yet, a variety of biological properties associated with the compounds found in BPs have been revealed by ongoing studies (Figure 1) [2].

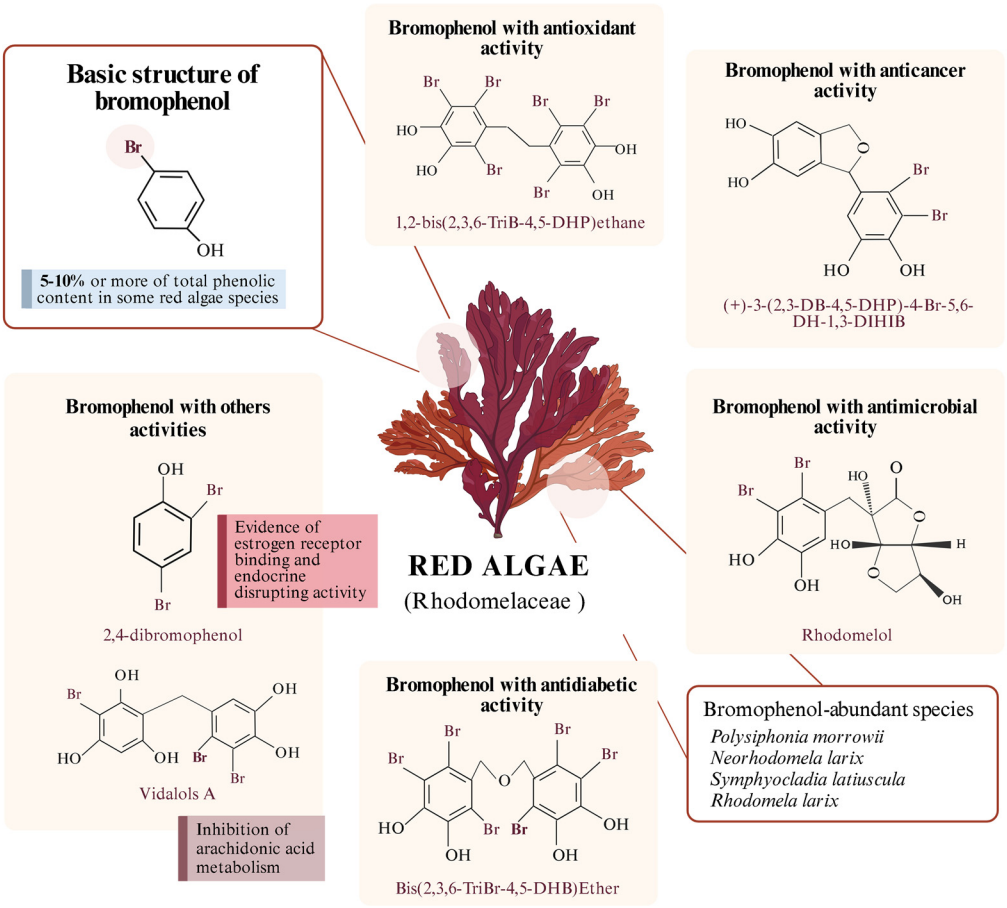

Figure 1. Some of the BPs that have exhibited certain outstanding biological properties [2]. Created with BioRender.com (accessed on 25 April 2024).

One of the most frequently mentioned compounds in the literature is 3-bromo-4,5-dihydroxybenzaldehyde (BDB), a natural active compound with demonstrated novel pharmaceutical applications and nutritional value [13]. Biological properties found in BPs from red algae include aldose reductase (AR) inhibition, antibacterial, anticancer, antifungal, antiviral, antiobesity and antidiabetic properties, anti-tyrosinase (TYR), carbonic anhydrase (CA) inhibition, antioxidant properties, and DPPH radical scavenging [3,14–18]. Moreover,

several BPs have shown antifeedant activity [19]. BPs are also involved in the defense and deterrent functions of the environment [7]. *Symphyocladia latiuscula*, known for adhering to a highly conserved biosynthetic pathway, was discovered for typically incorporating at least one 2,3,6-tribromo-4,5-dihydroxybenzyl moiety coupled with various functional groups such as aconitic acids, diketopiperazines, glutamines, pyrrolidin-2-ones, sulfoxides, sulfones, sulfates, and ureas [18]. Furthermore, these compounds can protect algae from stress, herbivores and antibiosis, as well as influence algal pigmentation [10]. These diverse biological properties of BPs highlight their great potential for biotechnological applications. Some of these applications in different biotechnological fields may be in the pharmaceutical, cosmetic and food industries [20].

2. Material and Methods

To investigate bromophenols (BPs) in macroalgae, a comprehensive systematic review was designed using reliable databases and high-impact journals. An exhaustive search was conducted across multiple platforms, including PubMed, Scopus, ScienceDirect, Google Scholar, and Web of Science. This search used specific inclusion criteria such as "have been published in the timeframe 2005–2024", "publication type: article, review or book chapter" or "include keywords: bromophenols, polyphenols, secondary metabolites, red algae" and was focused specifically on the chemical structure, properties, and biological activities of BPs.

These databases were selected for their extensive coverage of scientific literature and their ability to provide access to high-quality research articles. Emphasis was placed on articles published in the first (Q1) and second (Q2) quartiles to ensure the inclusion of reliable data and cutting-edge research. In addition, prioritizing studies with detailed methodologies and robust experimental designs ensured that only high-quality information was included in the analysis.

3. Chemical Structure and Properties: Extraction and Analytical Techniques

3.1. Bromination Variability and Its Impact on Properties

BPs are differentiated from other phenolic compounds by the presence of phenolic groups that are brominated to varying degrees [7]. These bromine atoms can be attached at different positions on the phenolic ring, leading to a diverse range of BP derivatives with distinct chemical properties. The degree of bromination affects the physical and chemical attributes of BPs, such as their solubility, reactivity and biological activity [7,19]. This special feature makes BPs valuable compounds in various applications, including pharmaceuticals, or natural products research [12].

3.2. Extraction and Analytical Techniques

BP extraction from red algae typically involves solid–liquid methods such as infusion, percolation, Soxhlet extraction, maceration, and steam distillation. These methods require long extraction times for optimal yield [7]. Organic solvents such as ethanol, methanol, methanol-dichloromethane, chloroform and hexane are also commonly used [21]. Conventional methods are based on heating mechanisms and are subject to optimization constraints due to various factors. Advanced practices such as ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), ultrasound-microwave-assisted extraction (UMAE), or supercritical fluid extraction (SFE) are moving toward sustainable extraction approaches to reduce environmental impact [22]. These green approaches employ environmentally friendly solvents such as ionic liquids and surfactants to enhance efficiency while meeting regulatory standards. While conventional methods dominate, research into sustainable techniques is essential to advancing the algae industry and promoting sustainable practices [23]. Advanced analytical techniques such as mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy are key to identifying BPs in red algae. Liquid chromatography coupled to MS (LC-MS) allows the precise separation and detection of these compounds from complex mixtures. Meanwhile, NMR spectroscopy, particularly

proton (^1H) and carbon (^13C) NMR, provides detailed structural information that aids in the characterization of BPs [24]. Other notable techniques utilized for identifying BPs include UV–VIS and photodiode array (PDA) detectors. Additionally, fluorimetric (FLD), colorometric arrays, and PDA coupled with fluorescence, along with chemical reaction detection techniques, are employed. Also, MS detectors, such as electrospray ionization mass spectrometry (ESI-MS), matrix-assisted laser desorption/ionization mass spectrometry (MALDI–MS), and fast atom bombardment mass spectrometry (FAB-MS), facilitate the structural characterization and confirmation of various BP classes. High-performance liquid chromatography (HPLC) coupled with MS detectors ensure high sensitivity and specificity, enabling accurate detection [22]. These techniques are essential for understanding the chemical composition and properties of BPs in red algae.

4. Biological Properties and Potential Applications

BPs from red algae have been proven to exhibit several biological properties that make them a natural choice for subsequent applications. These properties have been evaluated through *in vivo* and *in vitro* experiments. Table 1 shows additional details of these experimental studies. Nevertheless, some studies have challenged previous indications of efficacy. This reinforces the need to explore alternative properties or applications of these compounds, and to increase research in this area given the limited experimentation that has recently been conducted.

Table 1. Characteristics of the assays of BPs isolated from red algae.

Biological Property	Assay	Red Algae Species	Extraction Method	Compounds	Results Achieved	Potential Applications	Ref.
Antioxidant	DPPH	*Rhodomela confervoides*	95% EtOH	Ureido-BPs	DPPH (IC_{50} = 3.34 to 4.84 μM; AsA positive control 20.1 μM)	Drug discovery and development	[17]
Antioxidant	DPPH	*Polysiphonia urceolata*	95% EtOH	(3,5-Br2-4-OH-Ph) Ac-Butyl Est	DPPH (IC_{50} = 3.34 to 9.7 μM; BTH positive control 83.84 μM)	Multi-sectoral potential as a potent antioxidant	[25]
Antidiabetic	Enzyme inhibition	*Symphyocladia latiuscula*	95% EtOH	Compounds 1, 2, and 3	Aldose reductase inhibitory activity	Metabolic disease treatment	[8]
Antibacterial	Gingipain	*Kappaphycus alvarezii*	MetOH in H_2O 95:5%	Compounds A, B, and C	Potential of natural metabolites in controlling virulent proteins	Development of periodontal disease therapeutic approaches	[26]
Antimicrobial	MIC	*Odonthalia corymbifera*	Not specified	2,2′,3,3′-TetraBr-4,4′,5,5′-THDP	Strong activity against *C. albicans*, *A. fumigatus*, and *T. rubrum*	Antimicrobial agents for pharmaceutical and food preservation	[27]
Antimicrobial	CO-ADD	*Polysiphonia decipiens*	3:1 MetOH:CH_2Cl_2	BPs	Compounds from *P. decipiens* had no activity	No appreciable activity found	[28]
Antiobesity	Colorimetric	*Polyopes lancifolia*	95% EtOAc	C5	IC_{50} = 0.85 μM; Epigallocatechin gallate positive control 7.70 μM	Development of G6PD inhibitors for therapeutic use	[16]
Antiviral	Cell based	*Polysiphonia morrowi*	90% MetOH	3-Br-4,5-DHB-ME	IC_{50} = 19 μM; Ribavirin positive control 2.6 μM against IHN	Development of health-promoting animal feed and antiviral agents	[15]
Anti-inflammatory	OGD	ns	ns	BDB	BDB reduced ischemia-induced cytotoxicity and OS	Managing myocardial IR injury	[13]
Antitumor	MTT assays	*Leathesia nana*	95% EtOH	(2,3-DBE)	80.1% inhibition ratio	Therapeutic strategy for cancer treatment	[29]

Abbreviations: BPs: bromophenols; DPPH: scavenging a,a-diphenyl-b-picrylhydrazyl; IC_{50}: concentration required to reduce cell growth by 50%; ascorbic acid: AsA; BTH: butylated hydroxytoluene; Compound 1: 2,2′,3,6,6′-pentabromo-3′,4,4′,5-tetrahydroxydibenzyl ether; Compound 2: Bis(2,3,6-tribromo-4,5-dihydroxyphenyl)methane; Compound 3: 2,2′,3,5′,6-pentabromo-3′,4,4′,5-tetrahydroxydiphenyl-methane; Compound A: 3-bromo-5-(hydroxymethyl) benzene-1,2-diol; Compound B: 2,5-Dibromo-3,4-dihydroxybenzyl Alcohol; Compound C: 3,4-dibromo-5-(hydroxymethyl) benzene-1,2-diol; MIC: Minimal inhibitory concentration; CO-ADD: Community for Antimicrobial Drug Discovery; *C. albicans*: *Candida albicans*; *A. fumigatus*: *Aspergillus fumigatus*;

T. rubrum: *Trichophyton rubrum*; G6PD; glucose-6-phosphate dehydrogenase; IHNV: infectious hematopoietic necrosis virus; BDB: 3-bromo-4,5-dihydroxybenzaldehyde; OGD: *in vitro* model of oxygen and glucose deprivation; OS: oxidative stress; IR: ischemia and reperfusion; ns: not specified.

4.1. Enzymatic Activity

Three new BPs were discovered from the red alga *Symphyocladia latiuscula*, together with two BPs identified for the first time as natural products. These compounds showed significant aldose reductase inhibitory activity, suggesting their potential therapeutic application in the medical and pharmaceutical fields in the treatment of metabolic diseases such as diabetes [8]. In another study, novel BPs were assessed for their potential to inhibit acetylcholinesterase (AChE) and α-glycosidase. The results indicated that the BPs displayed Ki values between 8.94 and 59.45 nM for AChE and 4.31 to 44.14 nM for α-glycosidase, demonstrating greater potency than synthetic medications like donepezil (approximately 10 nM) and acarbose (around 50 nM). Furthermore, these BP derivatives showed significant antioxidant activity, outperforming conventional antioxidants such as ascorbic acid. Unlike many other marine natural products that typically exhibit lower efficacy and target single pathways, these BPs offer a promising multi-target therapeutic strategy for conditions like Alzheimer's disease and diabetes [4].

4.2. Antimicrobial and Antiviral Activity

A series of BPs showed promising antimicrobial activity against various pathogens. A specific compound showed remarkable efficacy against fungi, while synthetic derivatives showed potent antibacterial effects [27]. An antiviral *in vitro* study showed that fractions isolated from the red alga *Polysiphonia morrowii*, especially the 90% MeOH fraction, exhibited strong antiviral activity against infectious hematopoietic necrosis virus (IHNV) and infectious pancreatic necrosis virus (IPNV). This calls attention to the significant potential of BPs, such as 3-bromo-4,5-dihydroxybenzylmethyl ether and 3-bromo-4,5-dihydroxybenzaldehyde, as promising candidates for antiviral therapeutics [15]. Among the compounds isolated from *Polysiphonia urceolata*, (3,5-dibromo-4-hydroxyphenyl) acetic acid butyl ester exhibited the most potent scavenging activity against DPPH radicals with IC_{50} values ranging from 9.67 to 21.90 μM. These values were significantly lower than the positive control, butylated hydroxytoluene (BHT), which had an IC_{50} value of 83.84 μM. This newly discovered antioxidant compound from marine red algae has a wide range of potential applications [25].

4.3. Anti-Inflammatory Activity

In a study screening for anti-inflammatory activity, the protective effects of BDB against myocardial ischemia and reperfusion (IR) injury were investigated. Both *in vitro* and *in vivo* models showed that BDB attenuated ischemia-induced cytotoxicity, apoptosis, and oxidative stress. Moreover, BDB preserved mitochondrial function and increased mitochondrial antioxidant enzyme activities. Mechanistically, BDB activated the Akt-PGC1α-Sirt3 signaling pathway, which plays a critical role in mitochondrial biogenesis and antioxidant defense. These findings highlight the potential of BDB as a therapeutic agent to mitigate myocardial IR injury and suggest its promising role in the treatment of ischemic heart disease [13].

4.4. Antitumor Activity

As far as antitumor activity is concerned, BPs derivatives isolated from *Leathesia nana* displayed potent cytotoxicity against eight different cancer cell lines with IC_{50} values below 10 μg/mL. Moreover, all BPs demonstrated the inhibition of protein tyrosine kinase (PTK) with over-expression of c-kit, showing significant bioactivity with inhibition ratios of 70 and 80%. Additionally, EtOH extraction of *Leathesia nana* (EELN) demonstrated the ability to suppress Sarcoma 180 tumor growth and improve immune system indices *in vivo*. These data support the potential of BPs and EELN as antitumor agents and offer a promising treatment approach for cancer [14]. Furthermore, due to the resistance and

toxicity associated with traditional chemotherapy, the search for effective natural product candidates for the treatment of breast cancer is essential. A study demonstrated that XK-81, a novel BP derived from *Leathesia nana*, exhibited activity against 4T-1 breast cancer cells with an IC_{50} of 5.3 μM, primarily through the induction of ferroptosis. *In vivo* experiments showed that XK-81 reduced tumor growth by 58% in BALB/C mice and 52% in zebrafish models, while enhancing the immune response by increasing CD8-positive T cells and cytokine levels. Importantly, XK-81 demonstrated reduced cardiotoxicity compared to doxorubicin, resulting in a 20% reduction in heart damage, emphasizing its potential as a safer anti-tumor therapeutic [29].

5. Concluding Insights and Future Perspectives on Bromophenols

In conclusion, red algae-derived bromophenols exhibit a wide range of biological properties, including antioxidant, antimicrobial, antiviral, and anti-inflammatory activities, positioning them as promising candidates for therapeutic applications in various fields, particularly in pharmaceuticals and cancer treatment. Studies have shown that these compounds often exhibit greater potency and multi-target effects compared to traditional synthetic drugs, suggesting a potential advantage in efficacy and reduced side effects. Future perspectives for bromophenols include exploring their therapeutic potential in disease treatment, discovering new pharmacologically active molecules, investigating their applications in biotechnology and environmental management, and understanding their ecological role. Furthermore, the development of sustainable production methods through synthetic biology is essential. However, the current literature on bromophenols is limited, highlighting the need for further research and comprehensive studies to fully understand their potential. The lack of comprehensive literature highlights the need for increased research and documentation of these compounds to better inform future investigations and applications in the medical and scientific communities. Therefore, more clinical research needs to be carried out to realize its benefits and develop their full potential.

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