Research Advances on Secondary Metabolites from Marine Plants and Their Associated Microorganisms in the Beibu Gulf (Postprint)

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Abstract

Marine plants and their associated microorganisms constitute important components of marine life, capable of producing numerous secondary metabolites with novel structures and unique bioactivities that fulfill various physiological and ecological functions. The Beibu Gulf is rich in marine plant species resources, with statistical data indicating 43 species across 3 phyla. This review summarizes research progress on secondary metabolites from marine plants and their associated microorganisms in the Beibu Gulf since 2002. Specifically, 59 new compounds and 35 known bioactive compounds were isolated from 11 mangrove plant species and 7 associated microorganisms; 3 new compounds and 7 known bioactive compounds from 3 seagrass plant species; and 25 new compounds and 8 known bioactive compounds from 6 seaweed plant species and 1 associated microorganism. The main structural types encompass terpenoids, alkaloids, flavonoids, and sterols, most of which demonstrate favorable antibacterial, antioxidant, antitumor, anti-inflammatory, and immune-enhancing activities. Based on these findings, future research directions for marine plants in the Beibu Gulf and recommendations for subsequent studies are proposed. This review provides a reference for the in-depth investigation, development, and utilization of marine plants and their associated microorganisms in the Beibu Gulf.

Full Text

Preamble

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Research Progress on Secondary Metabolites of Marine Plants and Their Associated Microorganisms in the Beibu Gulf

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Abstract

Marine plants and their associated microorganisms constitute an important component of marine organisms, capable of producing numerous secondary metabolites with novel structures and unique activities that fulfill various physiological and ecological functions. The Beibu Gulf is rich in marine plant species resources, with statistics indicating 43 species across 3 phyla. This review summarizes research progress on secondary metabolites from marine plants and their co-epiphytic microorganisms in the Beibu Gulf since 2002. From 11 mangrove species and 7 associated microorganisms, 59 new compounds and 35 known bioactive compounds have been obtained; from 3 seagrass species, 3 new compounds and 7 known bioactive compounds; and from 6 algal species and 1 associated microorganism, 25 new compounds and 8 known bioactive compounds. The main structural types include terpenoids, alkaloids, flavonoids, and sterols, most of which exhibit promising antibacterial, antioxidant, antitumor, anti-inflammatory, and immune-enhancing activities. Based on these findings, future research directions and recommendations for subsequent studies are proposed. This review provides a reference for the in-depth research and development of marine plants and their associated microorganisms in the Beibu Gulf.

Keywords: Beibu Gulf, marine plant, marine microorganism, secondary metabolite, biological activity

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Introduction

The ocean covers approximately 71% of the Earth' s total surface area. Marine environments are characterized by extreme conditions such as low temperature, high pressure, low oxygen, oligotrophic nutrients, and high salinity. These unique environmental conditions have endowed marine organisms with enormous biodiversity, with over 200,000 species identified. Concurrently, marine organisms possess distinctive chemical diversity; as of 2019, more than 32,000 new compounds have been isolated and identified from marine sources, some representing entirely new structural classes (Carroll et al., 2021). Marine plants and their associated microorganisms, as crucial components of marine life, consistently contribute a substantial number of novel compounds. The unique structures and specific, potent bioactivities of marine natural products provide valuable insights for innovative drug design and development. To date,

17 marine-derived drugs have been approved as first-in-class international innovative drugs, with 8, 12, and 8 additional candidates in Phase I, II, and III clinical trials, respectively, and 4 more candidates approaching clinical trials (Wang et al., 2019). The China Food and Drug Administration has approved 9 marine drugs, 7 of which originate from marine algae: sodium alginate diester tablets, Haiqi Shugan, Haikun Shenxi, Gantangzhi, mannitol nicotinate tablets, Jiangtangning tablets, and Spirulina tablets. Among 13 marine drugs approved for clinical trials in China, 8 are derived from algae (Zhang et al., 2018; Feng et al., 2021). Therefore, research on bioactive compounds from marine plants and their symbiotic microorganisms remains a hotspot in marine natural product studies, providing a solid material foundation for developing innovative drugs.

The Beibu Gulf is located in the northwestern part of the South China Sea, bordered by Guangdong' s Leizhou Peninsula and Hainan Island to the east, Guangxi Zhuang Autonomous Region to the north, Vietnam to the west, and connected to the South China Sea via the Qiongzhou Strait. Situated in tropical and subtropical zones, the Beibu Gulf represents one of China' s most biodiverse marine regions and one of the richest areas for marine medicinal resources, offering unique advantages for marine drug research and development. Various marine plants in the Beibu Gulf have documented folk medicinal uses. Mangroves, growing in intertidal zones, are most commonly used by coastal residents, particularly by the Jing ethnic group, primarily for anti-inflammatory, heat-clearing, detumescence, and antidiarrheal purposes (Du et al., 2016). Seagrasses are used to treat fever, skin diseases, muscle pain, and prevent goiter (Kim, 2021). Algae are mainly employed for resolving phlegm, promoting diuresis, and reducing swelling (Gong et al., 2020). Marine plants in the Beibu Gulf primarily include three groups: mangroves, seagrasses, and algae, with bacteria and fungi as the main research targets among associated microorganisms. Although extensive research has been conducted on secondary metabolites from Beibu Gulf marine plants and their associated microorganisms over the years, comprehensive review articles are lacking. Existing reviews have broadly covered marine chemical constituents domestically, internationally, or in specific Beibu Gulf regions (Wang et al., 2004; Gao, 2011; Xu et al., 2020) without incorporating recent research findings. To provide a more comprehensive and in-depth understanding of research progress on secondary metabolites from Beibu Gulf marine plants and their associated microorganisms, this review systematically organizes, analyzes, and discusses literature reporting structurally novel and potently active secondary metabolites, offering reference materials for future research and effective development of these resources.

1. Secondary Metabolites from Mangroves and Their Associated Microorganisms in the Beibu Gulf

Mangroves are woody plants that grow in tropical and subtropical coastal intertidal zones, periodically inundated by seawater. Extensive mangrove forests are distributed across Beibu Gulf tidal flats, primarily in Lingao County, Danzhou

City, and Dongfang City in western Hainan; Leizhou Peninsula in Guangdong; Guangxi coastal areas; and northern Vietnamese coastal regions adjacent to Guangxi. Major Beibu Gulf mangrove reserves include Guangxi' s Shannan National Nature Reserve and Beilun Estuary National Nature Reserve, Hainan' s Caiqiao County-level Nature Reserve and Xinying Bay Municipal-level Nature Reserve, and Guangdong' s Zhanjiang National Mangrove Nature Reserve. The unique environment of high salinity, strong winds, high temperature, intense UV radiation, and oxygen-deficient mud in mangrove habitats promotes the production of numerous structurally novel secondary metabolites relevant to major human diseases in both mangrove plants and their associated microorganisms (Wu et al., 2008; Li et al., 2009).

1.1.1 Secondary Metabolites from *Aegiceras corniculatum*

Aegiceras corniculatum (family Myrsinaceae) is a common dominant mangrove species frequently used for analgesic, anthelmintic, and antibacterial purposes (Ning et al., 2013). Wang et al. (2006) isolated falcarindiol (1) from *A. corniculatum* branches collected in Beihai, Guangxi, which showed potent inhibitory activity against protein tyrosine phosphatase 1B (PTP1B), a target for Type II diabetes, with an IC_{50} value of 9.15 ± 2.48 mmol $\cdot$ L^{-1}. In combination with falcarinol, treatment with 1 reduced tumors larger than 3 mm by approximately 83% compared to the control group, demonstrating promising antitumor activity and positive effects against colorectal cancer (Morten et al., 2017). Resveratrol (2), another representative bioactive compound obtained from *A. corniculatum* by Wang et al. (2006), is a natural antioxidant (Salehi et al., 2018) with preventive effects against coronary and ischemic heart disease and tumor-inhibiting properties (Su et al., 2019; Alrafashr et al., 2020). Recent research has focused on the total synthesis of resveratrol using chemical and biological techniques. As shown in Figure 1 [Figure 1: see original paper], Ding et al. (2020) synthesized resveratrol starting from p-methoxycinnamaldehyde, which underwent aldol condensation with acetone under alkaline conditions, followed by demethylation, benzylation, cyclization, hydrolysis, decarboxylation, dehydrogenation, and deprotection, achieving an overall yield of 40% with potential for industrial production. Plant cell suspension culture technology has become the current industrial method for resveratrol production due to its low cost, high product quality, and minimal environmental impact (Li et al., 2009).

Wang et al. (2006) also isolated three new triterpenoid saponins from *A. corniculatum* leaves collected in Beihai: 3-O-[α-L-rhamnopyranosyl-(1$\rightarrow$2)$-$ $-L-$ $rhamnopyranosyl-(1\rightarrow2)-$ $-D-$ $galactopyranosyl-(1\rightarrow3)-$ $-D-$ $glucopyranosyl-(1\rightarrow2)-$ $-D-(6'-O-methyl)glucuronopyranosyl]-13,28-epoxy-3,16-dihydroxyolean(3)andthreeknowncompounds:(3,16,20)-3,16,28-trihydroxyolean-12-en-29-oicacid(1\rightarrow2)-O-[-D-glucopyranosyl(1\rightarrow4)]-$ $-L-$ $arabinopyranoside(4),3-O-$ $-D-$ $glucopyranosylaegicoroside A(5),andsakurasosaponin(6).Compounds4and5effectivelyinhibitedinflammato$ 12$p40, IL-6, and TNF-$, $with IC\_\{50\}$ values of 2.37 ± 0.46, 5.12 ± 0.58,

and 2.38 ± 0.31 $mol \cdot L^{-1}$, respectively. Compounds 3 and 6 significantly promoted apoptosis in B16F10 melanoma cells at 10 $mol \cdot L^{-1}$, suggesting potential for development as novel melanoma therapeutics. Compounds 5 and 6 exhibited antitumor activity, showing strong cytotoxicity against MCF7, A549, and HCT116 cell lines with IC_{50} values ranging from 2.89 ± 0.02 to 9.86 ± 0.21 $mol \cdot L^{-1}$ (Vinh et al., 2017).

1.1.2 Secondary Metabolites from *Acanthus ilicifolius* and Associated Microorganisms

Acanthus ilicifolius (family Acanthaceae) is distributed mainly in Hainan, Guangxi, and Fujian provinces of China, with traditional uses for anti-inflammatory, detumescence, stomachache, and cough treatments (Ning et al., 2013). Cai et al. (2017) isolated two new compounds, talaromyones A-B (7-8), and two known compounds, purpactin A (9) and tenellic acids A (10), from the endophytic fungus *Talaromyces stipitatus* obtained from *A. ilicifolius* leaves in Guangxi' s Shannan Mangrove National Nature Reserve. Compounds 8, 9, and 10 showed moderate α-glucosidase inhibitory activity with IC_{50} values ranging from 48.4 to 99.8 $mol \cdot L^{-1}$. Compound 8 exhibited antibacterial activity against *Bacillus subtilis* with a MIC value of 12.5 $g \cdot mL^{-1}$. Compound 9 acted as an inhibitor of TMEM16A-mediated Cl^- channels with an IC_{50} value of approximately 2 $mol \cdot L^{-1}$, potentially useful for treating mucus hypersecretion-related diseases (Chantapol et al., 2021). Compound 10 demonstrated anti-human hepatoma cell activity with an IC_{50} value of 62.1 $g \cdot ml^{-1}$ (Wen et al., 2006).

1.1.3 Secondary Metabolites from *Avicennia marina* and Associated Microorganisms

Avicennia marina (family Verbenaceae), also known as sea olive, exhibits contraceptive effects and is used to treat colds, dysentery, and sore throat. Yi Xiangxi' s research group conducted in-depth studies on antioxidant components from *A. marina* fruits collected in Beihai, Guangxi, obtaining four new phenylethanoid glycosides, marinoids F-I (11-14) (Yi et al., 2014), four new phenolic compounds, marinoids J-M (15-18) (Gao et al., 2014), one new caffeic acid derivative, maricaffeolylide A (19), and one new sterane derivative, maricyclohexene A (20) (Yan et al., 2015). Cellular antioxidant activity (CAA) assays revealed that compounds 14, 16, 17, and 19 displayed moderate antioxidant activity with EC_{50} values of 26, 23.0 ± 0.71, 36.2 ± 1.83, and 24 ± 0.3 $mol \cdot L^{-1}$, respectively. Further activity studies showed that compound 15 effectively improved cognitive impairment in vascular dementia (VD) rats; after treatment at 500 $mg \cdot kg^{-1}$, MDA levels decreased by 27.53%, NO levels decreased by 20.41%, GSH-Px activity increased by 11.26%, and SOD activity increased by 20.38% (Yi et al., 2020).

Lin Yongcheng' s research group (Pan et al., 2010) isolated one new lactone, 1,8-dihydroxy-10-methoxy-3-methyldibenzo[b,e]oxepine-6,11-dione (21), and

two new xanthone derivatives, 1-hydroxy-8-(hydroxymethyl)-6-methoxy-3-methyl-9H-xanthen-9-one (22) and 1-hydroxy-8-(hydroxymethyl)-3-methoxy-6-methyl-9H-xanthen-9-one (23), from the fungus *Phoma* sp. obtained from *A. marina* roots in Guangxi' s Shannan region. Compounds 21 and 22 showed no cytotoxic activity against human oral epidermoid carcinoma KB and KBv200 cells.

1.1.4 Secondary Metabolites from *Bruguiera gymnorrhiza* and Associated Microorganisms

Bruguiera gymnorrhiza (family Rhizophoraceae) is traditionally used to treat sore throat, diarrhea, abdominal pain, bleeding, and malaria (Xie et al., 2018). Guo Yuewei' s research group obtained a series of structurally novel sulfur-containing compounds from *B. gymnorrhiza* stems and leaves collected in Zhanjiang, Guangdong, and Guangxi' s Shannan Mangrove Reserve, including bruguiesulfurol (24), bruguiesulfoctanol (25), trans-3,3 -dihydroxy-1,5,1,5-tetrathiacyclodecane (26), cis-3,3' -dihydroxy-1,5,1 ,5 -tetrathiacyclodecane (27), and gymnorrhizol (28) (Sun et al., 2004; Liu et al., 2008; Huang et al., 2009). Compounds 24 and 28 are novel PTP1B inhibitors with IC_{50} values of 17.5 and 14.9 $mol \cdot L^{-1}$, respectively. The total synthesis of 28 was successfully achieved through reaction of Bunte salts with thiol metal salts (Figure 2 [Figure 2: see original paper]). Structure-activity relationship studies were conducted by replacing disulfide bonds with monosulfide bonds in the ring, and a four-step synthesis of bruguiesulfurol was developed (Figure 3 [Figure 3: see original paper]). During the synthesis of 28, Guo Yuewei' s team obtained a series of derivatives; compound 5a showed strong selectivity against other PTPs including TCPTP, while 7j exhibited the strongest PTP1B inhibitory activity with an IC_{50} value of 4.54 $mol \cdot L^{-1}$ (Gong et al., 2007).

Shang Suisheng (2006) isolated steviol (29) from *B. gymnorrhiza* bark collected in Hepu County, Guangxi, which showed good antitumor activity with an IC_{50} of 92 $g \cdot mL^{-1}$. Compound 29 inhibited α-glucosidase and HMG-CoA reductase with IC_{50} values of 68.75 and 44.99 $g \cdot mL^{-1}$, respectively (Zhang et al., 2021).

Gao Chenghai' s research group obtained a new alkaloid, gymnorrhizin A (30), from *B. gymnorrhiza* hypocotyls collected at Beilun Estuary in Guangxi, which showed IC_{50} values of 4.37 and 4.89 $mmol \cdot L^{-1}$ against hepatitis B surface antigen (HbsAg) and hepatitis B e antigen (HbeAg), respectively, with therapeutic index (TI) values of 2.68 and 2.40 (Chen et al., 2016). Known compounds scopoletin (31), secoisolariciresinol (32), and lyoniresinol-3α-O-β-D-glucopyranosides (33) showed weak inhibitory activity against the A549 tumor cell line with IC_{50} values of 290.2, 323.0, and 209.3 $g \cdot mL^{-1}$, respectively (Yi et al., 2013). Brugymnoside A (34) displayed high antioxidant activity with an EC_{50} value of 11.79 ± 0.78 $mol \cdot L^{-1}$ (Yao et al., 2017). Four new cyclohexylacetonitrile derivatives, menisdaurins B-E (35-38), exhibited significant anti-hepatitis B virus activity with EC_{50} values ranging from 5.1 ± 0.2 to 87.7 ± 5.8 $g \cdot mL^{-1}$ (Yi et al., 2015).

Lin Yongcheng' s group isolated one new compound, 8-hydroxyl-2-[1-hydroxyethyl]-5,7-dimethoxynaphtho[2,3-b]thiophene-4,9-dione (39), and five known compounds—8-O-methylbostrycoidin (40), anhydrojavanicin (41), 3β,5α-dihydroxy-(22E,24R)-ergosta-7,22-dien-6-one (42), NGA0187 (43), and beauvericin (44)—from the endophytic fungus *Aspergillus terreus* obtained from Guangxi *B. gymnorrhiza* branches. Compounds 40-41 and 43-44 significantly inhibited α-acetylcholinesterase with IC_{50} values of 2.01, 6.71, 1.89, and 3.09 $mol \cdot L^{-1}$, respectively. Compounds 42 and 44 showed cytotoxicity against MCF-7, A549, Hela, and KB cells with IC_{50} values of 4.98 and 2.02 $mol \cdot L^{-1}$ (MCF-7), 1.95 and 0.82 $mol \cdot L^{-1}$ (A549), 0.68 and 1.14 $mol \cdot L^{-1}$ (Hela), and 1.50 and 1.10 $mol \cdot L^{-1}$ (KB) (Deng et al., 2013a). Subsequently, a new compound, botryosphaerin F (45), was obtained, which inhibited MCF-7 and HL-60 cancer cell growth with IC_{50} values of 4.49 and 3.43 $mol \cdot L^{-1}$ (Deng et al., 2013b).

Chen et al. (2007) obtained one new biphenyl compound, 4 ,5-dihydroxy-2,3-dimethoxy-4-(hydroxypropyl)-biphenyl (46), from the endophytic fungus *Penicillium thomi* in Guangxi *B. gymnorrhiza* roots, which exhibited cytotoxic activity against A549, HepG2, and HT29 tumor cell lines with IC_{50} values of 10.1, 12.2, and 8.9 $mol \cdot L^{-1}$, respectively. Sun Chenghang' s group isolated compound (2R,3S,6S,7R,8R)-8-butyl-3-(3-formamido-2-hydroxybenzamido)-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-ylacetate (47) from *Streptomyces albidoflavus*, a white streptomycete from Guangxi Shannan mangrove *B. gymnorrhiza* leaves. Compound 47 showed MIC values of 0.01, 0.06, and 0.03 $mg \cdot mL^{-1}$ against tobacco brown spot fungus (*Alternaria alternata*), tomato gray mold (*Botrytis cinerea*), and tomato early blight (*Alternaria solani*), respectively, superior to the commercial fungicide Sha-ya-suo (Yan et al., 2010). Subsequently, 5,8-dienetetradecanoic acid (48) was obtained from this strain, showing strong nematicidal activity against *Caenorhabditis elegans* with an IC_{50} value of 162.8 $mg \cdot L^{-1}$ at a dose of 27.3 $mg \cdot L^{-1}$ (Tao et al., 2012).

1.1.5 Secondary Metabolites from *Excoecaria agallocha* and Associated Microorganisms

Excoecaria agallocha (family Euphorbiaceae) is traditionally used to treat constipation, skin ulcers, hand and foot swelling, and possesses aphrodisiac effects (Ning et al., 2013). Wang et al. (2004, 2005, 2006) obtained 10 new diterpenoid compounds, agallochaols A-F (49-58), from *E. agallocha* in Guangxi Shannan Mangrove National Nature Reserve. Li et al. (2010) isolated one new phenolic glycoside, 1-(3,5-dimethoxy-4-hydroxybenzyl)-6-O-galloyl-1-O-β-D-glucopyranoside (59), from *E. agallocha* collected in Beihai, Guangxi.

Li et al. (2016) isolated four new macrolides from the endophytic fungus *Lasiodiplodia* sp. obtained from *E. agallocha* in Guangdong' s Zhanjiang Mangrove National Nature Reserve: 7-oxolasiodiplodin (60), enantiomer of 8,9-dihydrogreensporone C (61), (R)-14-methoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclododecine-1,11,12-trione (62), and ethyl-2,4-

dihydroxy-6-(8 -hydroxynonyl)-benzoate (63). Compound 63 showed moderate cytotoxic activity against human monocytic lymphoma THP1, human metastatic breast ductal adenocarcinoma MDA-MB-435, human non-small cell lung cancer A549, human hepatocellular carcinoma HepG2, and human colorectal cancer HCT-116 cells, with IC_{50} values of 39.74, 10.13, 13.31, 12.50, and 11.92 $mol \cdot L^{-1}$, respectively. Other compounds showed no significant cytotoxic activity.

1.1.6 Secondary Metabolites from *Kandelia candel* and Associated Microorganisms

Kandelia candel (family Rhizophoraceae) is the most cold-tolerant mangrove species, widely distributed in Vietnam and China' s Guangdong, Guangxi, and Hainan provinces, traditionally used for hemostasis, burn treatment, and rheumatoid arthritis (Ning et al., 2013). Chen and Long (2006) isolated betulinic acid (64) and oleanolic acid (65) from *K. candel* stem bark in Guangxi Shannan Town, which showed weak cytotoxic activity against CNE-1 cells with IC_{50} values of 8,192 and 3,532 $g \cdot mL^{-1}$, respectively.

Liu et al. (2020) obtained two new compounds, talanaphthoquinone A-B (66, 67), and one known compound, 6-[1-(acetyloxy)ethyl]-5-hydroxy-2,7-dimethoxy-1,4-naphthalenedione (68), from the endophytic fungus *Talaromyces* sp. derived from *K. candel* embryos in Guangxi Shannan Town. Compound 68 reduced gene expression levels of pro-inflammatory cytokines interleukin-1, interleukin-6, and tumor necrosis factor (TNF)-α. Huang et al. (2013) isolated one new compound, α-pyrone meroterpene arigsugacin I (69), and two known compounds, arigsugacins F (70) and territrem B (71), from the endophytic fungus *Penicillium* sp. in *K. candel* leaves from Guangxi Shannan National Mangrove Reserve. All three compounds exhibited anti-acetylcholinesterase activity with IC_{50} values of 0.64 ± 0.08, 0.37 ± 0.11, and 7.03 ± 0.20 $mol \cdot L^{-1}$, respectively.

1.1.7 Secondary Metabolites from *Lumnitzera racemosa*

Lumnitzera racemosa (family Combretaceae) is traditionally used to treat diabetes, diarrhea, and malaria (Ning et al., 2013). Wang et al. (2006) isolated two active secondary metabolites, 2-methyl-1,3-dihydroxy-5-tridecylbenzene (72) and 1,3-dihydroxy-5-undecylbenzene (73), from *L. racemosa*, which inhibited protein tyrosine phosphatase 1B (PTP1B) with IC_{50} values of 13.38 ± 1.98 and 10.40 ± 0.88 $mol \cdot L^{-1}$, respectively.

1.1.8 Secondary Metabolites from *Sonneratia* Species

Sonneratia paracaseolaris and *S. apetala* (family Lythraceae) are used in folk medicine; the fruits are mashed into paste for hemostasis or sprain treatment, while leaves, flowers, and fruits decocted in water serve as internal medicine (Yi et al., 2013). Chen et al. (2011) obtained an α-alkylbutenolide dimer (74) from the methanol extract of *S. paracaseolaris* stem bark collected in Zhanjiang,

Guangdong, which showed excellent inhibitory activity against dual-specificity phosphatases with an IC_{50} value of 6.44 $mol \cdot L^{-1}$. Yi Xiangxi' s group isolated isorhamnetin (75), friedelin (76), and ursolic acid (77) from *S. apetala* fruits collected at Beilun Estuary in Guangxi, which showed antioxidant activity against HepG2 cells with EC_{50} values of 25.8 ± 1.3, 62.1 ± 3.5, and 45.2 ± 2.8 $mmol \cdot L^{-1}$, respectively (Yi et al., 2013). *S. apetala* fruit extracts effectively delayed aging and improved memory in mice (Li et al., 2019; Yi et al., 2019). Further investigation into the anti-aging components identified four new compounds, sonneradons A-D (78-81); compound 78 showed the most significant anti-aging effects on nematodes, increasing their lifespan by 30.83% ± 0.74% and 34.48% ± 0.92% at concentrations of 100 and 300 $mol \cdot L^{-1}$, respectively. Additionally, 78 significantly alleviated age-related reductions in pharyngeal pumping and body bending, indicating substantial potential for anti-aging applications. Molecular docking studies suggested that the HSF-1 pathway may be a key mechanism underlying the anti-aging effects of compound 78 (Yi et al., 2020).

1.2.1 Secondary Metabolites from *Cerbera manghas*

Cerbera manghas (family Apocynaceae) is mainly distributed in Guangdong, Guangxi, and Taiwan provinces of China, traditionally used as an emetic, purgative, and for surgical plasters and anesthetics. Deng et al. (2014) extracted a cardiac glycoside, (-)-17β-neriifolin (82), from *C. manghas* collected in Fangchenggang, Guangxi, which exhibited high contact toxicity against female adults, pupae, larvae, and eggs of red spider mites, with IC_{50} values of 0.28, 0.29, 0.28, and 1.45 $mg \cdot mL^{-1}$ within 24 hours, respectively.

1.2.2 Secondary Metabolites from *Myoporum bontioides* and Associated Microorganisms

Myoporum bontioides is a perennial shrub or tree used for dispelling wind and detoxification (Ye, 2014). Gu Wenxiang' s group identified compound 5,7-dihydroxyflavanone (83) from *M. bontioides* leaves collected in Leizhou Peninsula, Guangdong, which showed inhibitory effects against *Escherichia coli* and *Staphylococcus aureus* with a MIC value of 62.50 $g \cdot mL^{-1}$ (Dai, 2013; Ye et al., 2014). Tangeretin (84), sinensetin (85), dihydrokaempferol (86), and luteolin (87) exhibited good antifungal activity against banana anthracnose with IC_{50} values of 271.99, 159.22, 192.67, and 81.10 $g \cdot mL^{-1}$, respectively.

Wang et al. (2015) isolated two new cyclopentenone derivatives, (±)-(4R,*5S*,6S*)-3-amino-4,5,6-trihydroxy-2-methoxy-5-methyl-2-cyclohexen-1-one (88) and (±)-(4S*,*5S*)-trihydroxy-3-methoxy-4-methoxycarbonyl-5-methyl-2-cyclopenten-1-one (89), along with two new xanthone derivatives, 4-chloro-1,5-dihydroxy-3-hydroxymethyl-6-methoxycarbonyl-xanthen-9-one (90) and 2,8-dimethoxy-1,6-dimethoxycarbonyl-xanthen-9-one (91), from the endophytic fungus* Alternaria* sp. isolated from *M. bontioides* roots in Leizhou Peninsula. Compounds 88 and 89 showed effective ABTS scavenging activity with EC_{50} values of 8.19 ± 0.15 and 16.09 ± 0.01 $mol \cdot L^{-1}$, respectively. Compounds 89

and 90 exhibited MIC values of 215.52 and 107.14 $\mathrm{mol \cdot L^{-1}}$ against *Fusarium graminearum*, respectively, while 90 showed a MIC value of 214.29 $\mathrm{mol \cdot L^{-1}}$ against banana anthracnose fungus.

1.2.3 Secondary Metabolites from *Pongamia pinnata* and Associated Microorganisms

Pongamia pinnata (family Fabaceae) is traditionally used as an emetic and for treating tinea, scabies, sores, and diabetes (Ning et al., 2013). Tan et al. (2018) found that *P. pinnata* ethanol extracts inhibited proliferation of prostate cancer DU145 and PC3 cells. Three new compounds were obtained from the endophytic fungus *Nigrospora* sp. in Guangxi *P. pinnata* stem tissues: 6-O-desmethyldechlorogriseofulvin (92), 6 -hydroxygriseofulvin (93), and 2,3-didehydro-19a-hydroxyl-14-epicochlioquinone B (94). Compound 94 showed strong cytotoxic activity against human breast cancer MCF-7, pancreatic cancer SW1990, and liver cancer SMMC7721 cell lines with IC_{50} values of 4, 5, and 7 $\mathrm{g \cdot mL^{-1}}$, respectively (Zhou et al., 2012).

2. Secondary Metabolites from Seagrasses in the Beibu Gulf

Seagrasses are monocotyledonous plants growing in shallow waters of tropical and temperate seas, with 72 species globally (Duffy et al., 2019). China hosts 22 seagrass species across 10 genera and 4 families, accounting for approximately 30% of global seagrass diversity. Seagrass secondary metabolites exhibit antibacterial, antioxidant, and antifouling activities (Kim, 2021). Current research has focused on secondary metabolites from *Potamogetonaceae* genera (*Zostera*, *Syringodium*, *Halodule*) and *Hydrocharitaceae* (*Halophila*) in the Beibu Gulf (Zheng et al., 2013). Bu (2015) isolated two flavonoids, apigenin-7-O-β-glucoside (95) and chrysoeriol-7-O-β-glucoside (96), from *Halophila* collected in Beihai, Guangxi. Both 95 and 96 showed hydroxyl radical scavenging capacity with IC_{50} values of 0.53 and 0.44 $\mathrm{g \cdot mL^{-1}}$, respectively. Studies indicated that 95 also inhibited HIV replication, demonstrating anti-HIV bioactivity (Li & Peng, 2013). Qi Shuhua' s group isolated luteolin (87), daucosterol (97), and hexacosanol (98) from *Enhalus acoroides* collected in Hainan, which showed cytotoxicity. Compounds 97 and 98 inhibited marine bacterium *Loktanella hongkongensis* with inhibition zones of 3.10 $\pm$ 0.59 and 4.25 $\pm$ 0.67 mm, respectively. Luteolin (87), 98, and luteolin-4 -glucuronide (99) showed weak inhibitory activity against seven marine fouling indicator bacteria including *Pseudoalteromonas piscida*, *Rhodovulum* sp., *Ruegeria* sp., *Vibrio alginolyticus*, *V. furnissii*, *V. halioticoli*, and *V. harveyi*, with inhibition zones ranging from 2.00 $\pm$ 0.17 to 3.34 $\pm$ 0.44 mm. Compound 99 significantly inhibited bryozoan activity with an EC_{50} value of 0.52 $\mathrm{g \cdot mL^{-1}}$ (Qi et al., 2008). Additionally, a new phenylethane derivative, (s)-methoxy-(3 ,5 -dimethoxy-4 -hydroxyphenyl)ethaneiol (100), was isolated from *Thalassia hemprichii* collected in Lingshui County, Hainan (Qi et al., 2012). Wang et al. (2019) isolated two novel diterpenes, enhoidin A (101)

and enhoidin B (102), from *E. acoroides*; compound 101 showed low cytotoxic activity with IC_{50} values of 40–100 $g \cdot mL^{-1}$, while 102 was inactive ($IC_{50} >$ 77 $g \cdot mL^{-1}$). Zhu et al. (2019) obtained luteolin-7-O-glucuronide (103) from *E. acoroides*, which showed algicidal activity with an EC_{50} of 34.29 $g \cdot mL^{-1}$, suggesting potential as a novel algicide.

3. Secondary Metabolites from Algae and Their Associated Microorganisms in the Beibu Gulf

The Beibu Gulf harbors diverse and abundant seaweed resources across three phyla: Ochrophyta (brown algae), Rhodophyta (red algae), and Chlorophyta (green algae), with red algae being the most species-rich and green algae the least (Ding et al., 2014).

3.1 Secondary Metabolites from Brown Algae and Associated Microorganisms

Sargassum confusum (order Fucales, family Sargassaceae) is used for hemostasis, phlegm elimination, and fever reduction, with high medicinal value (Li et al., 2017). Tang et al. (2002) isolated gomisin N (104), 132S-hydroxypheophytin a (105), and pheophytin a (106) from brown alga *S. carpophyllum* in Beihai, Guangxi. Compounds 104-106 induced morphological changes in *Pyricularia oryzae* mycelia with minimum morphological concentrations of 157, 282, and 287 $mol \cdot L^{-1}$, respectively. Compound 104 inhibited human promyelocytic leukemia HL-60 cells with an IC_{50} of 4.8 $g \cdot mL^{-1}$. At 20 $g \cdot mL^{-1}$, compounds 105 and 106 inhibited human breast cancer MCF-7 cells by 43% and 10%, and human lung cancer A549 cells by 24% and 9%, respectively. Compound 106 inhibited various human cancer cells and demonstrated photodynamic effects against different cancer types under 14 $J \cdot cm^{-2}$ light radiation, with IC_{50} values of 70–200 $nmol \cdot L^{-1}$, showing particular promise against prostate cancer; combined photodynamic therapy (PDT) treatment reduced human prostate cancer PC-3M cell viability to approximately 10% (Xie et al., 2021). Xu et al. (2002) isolated a new compound, stigmasta-3β-hydroxy-5,23,25-triene (107), from *S. polycystum* in Beihai, Guangxi. *Sargassum thunbergii*, a warm-temperate seaweed endemic to the western North Pacific and commonly distributed from the Liaodong Peninsula to Leizhou Peninsula in China, yielded compounds with brine shrimp lethality: 2-[(3S,7S,11S)-3-hydroxy-3,7,11,15-tetramethylhexadecyl]-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione (108), ecdysterone (109), and ergosterol peroxide (110) (Jin et al., 2011). At 25 $g \cdot mL^{-1}$, these compounds caused 54.3%, 44.5%, and 45.5% brine shrimp mortality, respectively. Compound 110 also showed moderate toxicity to zebrafish embryos with a 72-h EC_{50} of 21.7 $g \cdot mL^{-1}$. Peng et al. (2018) isolated a new isoprenoid derivative, sargassumone (111), and the known norisoprenoid (+)-epiloliolid (112) from brown alga *S. naozhouense* along the Beibu Gulf coast of Leizhou Peninsula. Compound 111 showed DPPH radical scavenging activity with an EC_{50} of 17 ± 0.35 $mmol \cdot L^{-1}$ and inhibition zones

of 6.50 ± 0.20, 8.20 ± 0.11, and 7.00 ± 0.20 mm against *Candida albicans*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Escherichia coli*, respectively.

Yang et al. (2006) obtained two new macrolides, 6-oxo-de-O-methyllasiodiplodin (113) and (E)-9-etheno-lasiodiplodin (114), from an endophytic fungus (*Sargassum* sp.) in brown alga *Sargassum* from Zhanjiang, Guangdong.

3.2 Secondary Metabolites from Red Algae

Guan (2020) isolated a new pyrrolidone alkaloid, (R,E)-4-ethylidene-3-hydroxy-3-methylpyrrolidine-2,5-dione (115), and a new monoterpene lactone, isololiolide A (116), from *Acanthophora spicifera* in Xuwen, Zhanjiang. Compound 116 exhibited cytotoxicity, inducing apoptosis in liver cancer cells through caspase-3 activation, decreased Bcl-2 levels, increased p53 expression, and PARP cleavage (Catarina et al., 2016). Lin et al. (2020) obtained a new pyrrolidone alkaloid, acanthophoraine A (117), from the same *A. spicifera* location.

3.3 Secondary Metabolites from Green Algae

Liu et al. (2012) isolated 12 new compounds from *Caulerpa racemosa* collected in the South China Sea off Zhanjiang, Guangdong: racemosols A-C (118-120), racemosol D (121), racemosins A-C (122-124), caulerchlorin (125), (23E)-β-sitost-23-ene-28-one (126), (8E,12Z,15Z)-10-hydroxy-8,12,15-octadecatrien-4,6-diynoic acid (127), and caulerterpenoids A-B (128-129). Compound 125 showed inhibitory activity against *Cryptococcus neoformans*. Li et al. (2020) isolated six new compounds from *C. racemosa* in Xuwen County, Zhanjiang: caulerpalide A (130), (+)-caulerpalide B (131), (-)-caulerpalide B (132), caulerine A (133), and caulerspiro A-B (134-135). Ursolic acid (136) showed significant inhibitory effects against *Enterococcus faecalis* and *Staphylococcus aureus* with MIC values of 8 and 32 $\mathrm{g \cdot mL^{-1}}$, respectively.

4. Conclusion

The Beibu Gulf is one of China' s most biodiverse marine regions, and its marine plants and associated microorganisms constitute an important component of national marine resources. This review summarized research progress on secondary metabolites from Beibu Gulf marine plants and their associated microorganisms, reporting a total of 136 compounds: 37 new and 24 known compounds from 11 mangrove species; 22 new and 11 known bioactive compounds from 7 mangrove-associated microbial strains; 3 new and 7 known bioactive compounds from 3 seagrass species; 22 new and 9 known compounds from 6 algal species; and 2 new compounds from algal-associated microorganisms. As shown in Figure 4 [Figure 4: see original paper], statistical analysis indicates that mangroves and their associated microorganisms represent the hottest research topic in recent years, accounting for the highest proportion of secondary metabolites. This

correlates with their relative species abundance, convenient tidal flat accessibility, and extensive folk medicinal use. Research on seagrasses and algae with their associated microorganisms remains relatively limited, likely due to seasonal availability, sampling difficulties, and requirements for specialized transportation and collection equipment, all of which impact research progress. Despite later initiation, algae and their associated microorganisms show the highest proportion of new metabolites. Current research on algae and associated microorganisms primarily focuses on macroalgae, with microalgae and their associated microorganisms largely unexplored—representing an important future direction in marine natural product research.

Analysis of secondary metabolite structures and quantities from Beibu Gulf marine plants and associated microorganisms (Figures 5 [Figure 5: see original paper] and 6 [Figure 6: see original paper]) reveals that terpenoids, flavonoids, lactones, steroids, alkaloids, and phenolic acids predominate. Numerous structurally novel and potently active compounds continue to be discovered, attributable to the high-salt, high-temperature, and low-oxygen marine environments inhabited by these organisms. This structural diversity provides expanded possibilities for new drug discovery. Correlation between secondary metabolite structures and activities demonstrates that most compounds possess promising antibacterial, anti-inflammatory, antioxidant, antitumor, cardiovascular therapeutic, and immunomodulatory functions. Mangrove secondary metabolites exhibit particularly diverse activities, likely because mangrove plants have extensive folk medicinal records in the Beibu Gulf, enabling more targeted research. For example, *B. gymnorrhiza* is traditionally used for heat-clearing and detoxification, with Jing ethnic medical texts documenting its use for hepatitis B, leading to the isolation of alkaloids and nitriles with anti-hepatitis B activity. *L. racemosa* is used for diabetes, yielding steroidal compounds with PTP1B inhibitory activity. *A. marina* is used for cold prevention and immunity enhancement, resulting in the isolation of phenylethanoid glycosides and new phenolic compounds with antioxidant and anti-inflammatory effects. Studies on mangrove chemical constituents and pharmacological activities have provided references for drug development, including the natural antioxidant resveratrol from *A. corniculatum*, PTP1B inhibitors from *B. gymnorrhiza*, new phenolic compounds improving VD rat cognitive function, and phenylethanoid glycoside tablets for cardiovascular dementia from *A. marina*. Seagrass secondary metabolites are primarily flavonoids, phenolics, and lipids with antibacterial and free radical scavenging activities. Algae mainly contain polysaccharides, polyphenols, and terpenoids with antioxidant, antibacterial, immunomodulatory, antitumor, anticoagulant, and hypoglycemic activities. Marine plant-associated microorganisms have emerged as a recent research hotspot, predominantly fungi, bacteria, and actinomycetes producing alkaloids, terpenoids, phenolic acids, and sterols with antitumor, antibacterial, anti-inflammatory, and insecticidal activities. The rich structural diversity of secondary metabolites presents multiple pharmacological activities, making structure-activity relationship studies and druggability evaluations of

significantly active compounds a current hotspot, providing lead compounds for novel drug development.

5. Outlook

The Beibu Gulf, located in tropical and subtropical zones, hosts China' s largest mangrove area and multiple seagrass bed ecosystems, both harboring abundant marine microbial communities. The international marine drug field currently focuses on structurally novel and active compounds from marine microorganisms, representing a major research trend (Ma et al., 2021). China leads globally in oligosaccharide drugs from marine macroalgae, yet Beibu Gulf marine plant oligosaccharide research remains largely unreported. Researcher Wu Jun from Southern Medical University discovered Benthol A, a new super-carbon-chain compound family member, from a new benthic dinoflagellate species in the South China Sea (Jiang et al., 2021), indicating vast research potential in medium-molecular-weight compounds from marine microalgae.

The marine biopharmaceutical industry is a crucial component of the ocean economy and a strategic emerging industry with enormous potential, with a compound growth rate double that of the overall marine production value, making it the fastest-growing marine industry sector in the past decade. Research on bioactive secondary metabolites from Beibu Gulf marine plants and their associated microorganisms forms the foundation and core of the marine biopharmaceutical industry. While scholars have achieved numerous research results, significant challenges remain, including sampling difficulties, scarce sample quantities, halted pharmacological studies due to insufficient compound quantities, lack of druggability or clinical studies, disconnection between theoretical research and practical applications, and limited application of new technologies. Therefore, rationally utilizing Beibu Gulf' s sustainable marine plant resources to discover more valuable marine drugs is particularly important. We propose seven directions for future research: (1) Continue rational development and utilization of Beibu Gulf marine plants to deeply explore secondary metabolites, obtain more structurally novel compounds, expand activity screening scope, deepen activity detection levels, and investigate mechanisms of action; (2) Conduct chemical or biosynthesis studies on secondary metabolites with significant activity, novel structures, and clear mechanisms to completely solve the problem of insufficient drug sources for preclinical or clinical studies; (3) Fully explore marine plant-associated microbial species, expand the Beibu Gulf marine drug library, and increase candidate drug varieties through in-depth studies on marine microbial bioactive secondary metabolites; (4) Integrate resources from research institutions, pharmaceutical companies, and hospitals within and outside the region, promote full collaboration among industry-academia-research-application units, and enhance druggability and clinical studies of significantly active secondary metabolites from Beibu Gulf sources; (5) Oligosaccharide drugs are currently an international research hotspot, while Beibu Gulf marine plant oligosaccharide secondary metabolite research is still in its infancy—more attention should

be paid to this area; (6) Conduct taxonomic studies on Beibu Gulf marine microalgae, establish laboratory culture systems, and initiate research on medium-molecular-weight compounds from Beibu Gulf marine microalgae; (7) Artificial intelligence (AI) has been widely applied in key pharmaceutical research areas including target drug discovery, compound screening, ADMET property prediction, drug crystal form prediction, pathobiology research, and drug repurposing, yielding 事半功倍 (twice the result with half the effort) outcomes. Therefore, AI should be deeply integrated into the discovery of novel secondary metabolites and innovative drug druggability and clinical studies from Beibu Gulf marine plants and their associated microorganisms to accelerate innovative drug research progress.

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Note: Figure translations are in progress. See original paper for figures.