Ocean & seas: Novel biomedical resources for anti-infection of SARS-CoV-2

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Abstract

This article briefly reviews ocean and seas as huge and novel biomedical resources for anti-infection, which includes tuberculosis, H. Pylori, and HIV infection as well as SARS-CoV-2, and as promising biomedical resources for infection-induced major non-communicable diseases (mNCDs), such as cardiovascular disease, diabetes, and cancer. These marine natural products (MNPs) and organisms include sea cucumbers, sea snake, sponge, marine algae and microalgae, etc. As key biomedical resources for the discovery of marine drugs, bioactive molecules, and agents for treatment of infectious diseases and mNCDs, MNPs have bioactive potentials of antioxidant, anti-infection, anti-inflammatory, anticoagulant, anti-diabetic effects, and cancer treatment. In addition, their anti-inflammatory mechanisms for infectious diseases are also involved. It's time to protect ocean ecosystem for human better sustainable development in the new era of ocean economy.

Introduction

According to a comprehensive survey of deep coral reefs in the high seas, researchers think that policymakers should give more attention to protection of ocean ecosystems and marine mammals [1, 2]. Whether the United Nations Ocean Conference in Lisbon in 2020 will be rescheduled in 2021 or not, there aren't yet the answer [3]. But it should be a priority for the future of this global ecosystem due to a linkage with sources of sustainable food, energy, materials, biomedicine, and many others.

Currently, ocean economy is accelerating development in the globe and has become a vital support for human sustainable development. Marine organisms have been considered as promising biomedical resources, marine drugs have long been used and exhibit unique advantages in clinical practices. Hence, it is a great task to protect and develop ocean resources and prevent and control ocean pollution since some compounds are valuable tools in biomedicine and applications [4, 5].

Ocean & seas: Huge biomedical resources for anti-infection

As biomedical scientists, we know that marine products are beneficial to human health. The scientists are developing chemicals and novel therapeutic drugs from marine natural products (MNPs) with anti-tuberculosis activity and H. pylori infection [6, 7], and defensive effects against viral infection, including the SARS-CoV-2 and HIV-1 [8, 9]. We expect that these compounds could be employed to treat and prevent infectious diseases, including COVID-19 and AIDS, if truly having significant antiviral activities. However, there are still huge challenges in the discovery and development of marine drugs.

The crude extracts from marine organisms contain compounds capable of inhibiting inflammation and potential bioactive molecules [10]. Echinochrome pigment extracted from sea urchin has an insightful antiulcer healing effect [11]. Bis (3-bromo-4,5-dihydroxybenzyl) ether (BBDE, $C_{14}H_{12}Br_2O_5$), a novel bromophenol isolated from the red alga Polysiphonia morrowii [12], is useful for treating inflammatory diseases due to the

inhibition of LPS-induced inflammation in macrophage cells by inhibiting the ROS-mediated ERK signaling pathway and reducing inflammatory mediators.

As we known, MNPs are important biomedical resources for anti-infection. There are more than 1600 new steroidal structures isolated from marine organisms. Some steroids can regulate the farnesoid X receptor (FXR) and the pregnane X receptor (PXR). Novel FXR and PXR agonists and antagonists can target human diseases, e.g., intestinal inflammation [13]. Marine invertebrate glycans (ascidians and sea cucumbers) could be used as starting material for new therapeutics due to anticoagulant activity and anti-inflammation [14].

Sea cucumbers are widely consumed in traditional medicine and food. Holothuria grisea agglutinin (HGA) has demonstrated the ability to modulate the inflammatory response in models of inflammation in vivo. Moreover, it is the first marine invertebrate lectin that showed an anti-inflammatory effect [15]. Fucosylated chondroitin sulfate (fCS) extracted from the sea cucumber Holothuria forskali, as an inhibitor of selectin interactions, plays vital roles in inflammation and metastasis progression [16]. Sea cucumbers-derived sterol sulfate effectively attenuated inflammation by increasing serum adiponectin and reducing pro-inflammatory cytokine release [17].

A novel cathelicidin (Hc-CATH) from the sea snake Hydrophis cyanocinctus, has potent both antimicrobial and anti-inflammatory activity by inhibiting the LPS-induced production of nitric oxide (NO) and pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, is a potent candidate for the development of peptide antibiotics [18]. A small-molecule compound isolated from marine-derived fungus, bis-N-norgliovictin, significantly inhibits lipopolysaccharide (LPS, ligand of TLR4)-induced tumor necrosis factor-α (TNF-α) production, and exhibits potent anti-inflammatory effect both in vitro and in vivo [19]. Hence, it can be a useful therapeutic candidate for the treatment of sepsis and other inflammatory diseases.

As a novel marine metabolite isolated from the sponge Fasciospongia cavernosa, Cacospongionolide B showed topical anti-inflammatory activity and reduced the inflammatory response of adjuvant arthritis [20], could be used as new anti-inflammatory agents. Four drug candidates from novel bioactive sponge [21]: IPL576,092, HTI-286 (Taltobulin), EPI-506 (Ralaniten acetate), and AQX-1125, can be used for treatment of not only inflammation but also cancer.

As bioactive molecules with the anti-inflammatory activity, microalgae-derived Oxylipins (OXLs) have the therapeutic potential in inflammatory diseases [22], could act as agonist of PPAR-γ and consequently inhibit NFאB signaling pathway activation, thus lowering the production of inflammatory markers. Avarol is a marine sesquiterpenoid hydroquinone with anti-inflammatory and antipsoriatic properties [23], it inhibits several key biomarkers up-regulated in the inflammatory response of psoriatic skin. The marine compound didemnin B decreases the activity of the cell types implicated in liver inflammation and fibrosis in vitro [24].

Ocean & seas: Novel biomedical resources for anti-SARS-CoV-2

As an enveloped RNA virus, coronavirus is a major cause of human respiratory diseases. The spike glycoprotein (SGP) is known as the main target of antibodies having neutralizing potency and is also considered as an attractive target for therapeutic or vaccine development. MNPs as key and novel biomedical resources for the discovery of drugs to combat the COVID-19 pandemic, will be more and more valuable.

Among MNPs library, 17 potential SARS-CoV-2 main protease (M^{pr}) inhibitors have been identified by structure-based techniques, and one of these compounds could be bioactive [25]. Marine bacteria and fungi-derived bioactive 15 compounds showed promising potential roles against SARS-CoV-2 RNA dependent RNA polymerase (RdRp) and methyltransferase (nsp16) [26]. Some new MNPs compounds (bioactive peptides) isolated from marine organisms (such as vertebrates, invertebrates, seaweeds, or sea microorganisms) have a role of prevention on SARS2-Cov infection due to potential ACE inhibition and anti-hypertensive activities [27].

For example, some bioactive agents from marine polysaccharides and polysaccharide-based vaccine adjuvants were developed for the fight against SARS-CoV-2 and were used as therapeutic agents and vaccines of COVID-19 [28]. A naturally existing sulfated polysaccharide, lmbda-carrageenan (λ-CGN), purified from

marine red algae, could be a promising antiviral agent for preventing infection with several respiratory viruses since this polyanionic compound exerts antiviral activity by targeting viral attachment to cell surface receptors and preventing virus entry [29]. Novel marine sulfated polysaccharides can be developed further for prophylactic as well as therapeutic purposes due to potent anti-SARS-CoV-2 activity and affinity to the SGP [30].

Carbohydrate-binding agents (CBAs) from MNPs like lectins from marine algae have shown antiviral activities against SARS-CoV-2 due to targeting of N-linked glycans of the SGP envelope of CoV, and could also serve as an attractive therapeutic approach for developing novel antivirals [31]. As SARS-CoV-2 M^{pro} inhibitors, five MNPs (a benzo[f]pyrano[4,3-b]chromene, notoamide I, emindole SB beta-mannoside, and two bromoindole derivatives) were the most promising marine drug-like leads [32].

Up-to-date, FDA-approved marine drugs have the potential to inhibit the biological activity of SARS-CoV-2 main protease since they can bind at its active site and displace water molecules at this site [33]. The nontoxic and non-immunogenic polyphosphate (polyP), a physiological, metabolic energy (ATP)-providing polymer, could possibly also exert a protective effect against SARS-CoV-2-cell attachment [34].

Thus, these marine drugs which are already in clinical use for cancer treatment can also be used as a potential alternative to prevent and treat infected individuals with SARS-CoV-2. Hence, the MNPs and their derivatives could be a promising source of structurally diverse new anti-RNA virus therapeutics [35].

Ocean & seas: Promising biomedical resources for infection-related mNCDs

Generally speaking, chronic or acute infection highly links with cardiovascular disease (hypertension, myocardial infarction, arrhythmia, heart failure, and stroke), diabetes, cancer, respiratory and renal diseases as well as the related CDC strips or Re-CDC strips [36, 37]. Some MNPs have numerous health benefits, such as antioxidant, anti-infection, anti-inflammatory, anticoagulant, anti-diabetic effects, and cancer treatment [38, 39]. Thus, marine drugs are not just suitable for infectious diseases, but also for prevention and treatment major noncommunicable diseases (mNCDs).

A study found that mineral-balanced deep sea water [magnesium (Mg):calcium (Ca)=3:1] (MB-DSW) has anti-atopic dermatitis activity due to regression of inflammatory chemokines [40]. Other studies found that MB-DSW has anti-diabetic and anti-obesity action [41] due to the stimulatory effect on mitochondrial biogenesis and function and enriched with Mg and Ca, and the effects on cholesterol metabolism [42] due to prevention of the high glucose- or FFA/glucose-induced increase of cellular cholesterol levels (is its potential just like statin drugs?), and the role of the prevention of ultraviolet light-induced skin cancer development [43] due to enhancing skin cell clearance through the activation of autophagic cell death.

In addition, recombinant photoproteins from different marine organisms as a promising analytical tool have a big role in biomedical research fields [44], such as the measurement of Ca^{2+} in different intracellular compartments of animal cells, as labels in the design and development of binding assays as well as the emerging use of bioluminescence.

Conclusion and Prospects

Totally, this is a new era of ocean economy since biomedicine and particularly AIDS research are indeed a growth industry [45]. The microbial flora, for example, K. pneumoniae HSL4 [46], is highly associated with industrial applications, this microbial fermentation and related biosynthesis could be also used in the field of biomedicine. New biomedical resources and novel biotechnologies will help to control and combat the current COVID-19 pandemic [47]. Whatever, MNPs are worthy of developing biomedical agents for universal health coverage when combined with a magic "polypill"— "environment-sleep-emotion-exercise-diet" intervention [E(e)SEEDi] [48].

However, marine radioactivity is a threat to human health or the environment [49]. Thus, ocean environment and marine microbes play strong roles in healthy ecosystems [50, 51]. Moreover, there are correlations between an ocean-atmosphere and human health [52], environmentally acquired infections and human disease

[53, 54]. Hence, only healthy ocean and seas can meet human hope in the future. It's time to protect ocean ecosystem for human better sustainable development.

Currently, due to the challenge of malnutrition (undernutrition and overnutrition) in China [55], for example, having suboptimal intakes of seafood [56], as food lovers [57], we should improve nutrition status with effective strategies. Since there is a link between nutrition status and COVID-19 [58], we should assess positively the nutritional risks in COVID-19 cases with useful tools [59, 60], so as to promote nutritional care and the nutrition management in these patients [61]. And by the online-to-offline (O2O) food delivery [62] during the COVID-19 pandemic, people will combat effectively the SARS-CoV-2 and its variants.

Abbreviations

Carbohydrate-binding agents (CBAs); fCS: Fucosylated chondroitin sulfate; FXR:

farnesoid X receptor; HGA: Holothuria grisea agglutinin; MB-DSW:

mineral-balanced deep sea water; mNCDs: major non-communicable diseases; MNPs:

marine natural products; NO: nitric oxide; lipopolysaccharide (LPS); O2O:

online-to-offline; PXR: pregnane X receptor; RdRp: RNA dependent RNA

polymerase; SGP : spike glycoprotein; TNF-α: tumor necrosis factor-α.

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