Marine natural products and human immunity: Novel biomedical resources for anti-infection of SARS-CoV-2 and related cardiovascular disease

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Abstract

Major marine natural products (MNPs) and marine organisms include sea urchin, sea squirts or ascidians, sea cucumbers, sea snake, sponge, soft coral, marine algae, and microalgae. As vital biomedical resources for the discovery of marine drugs, bioactive molecules, and agents for treatment of infectious diseases and major non-communicable diseases (mNCDs), these MNPs have bioactive potentials of antioxidant, anti-infection, anti-inflammatory, anticoagulant, anti-diabetic effects, cancer treatment, and improvement of human immunity. This article reviews MNPs as huge and novel biomedical resources for anti-infection of coronavirus, SARS-CoV-2 and its major variants (such as Delta and Omicron), as well tuberculosis, H. Pylori, and HIV infection, and as promising biomedical resources for infection related cardiovascular disease (irCVD), diabetes, and cancer. The anti-inflammatory mechanisms of current MNPs against SARS-CoV-2 infection are also involved. Moreover, since the use of other chemical agents for COVID-19 treatment are associated with some adverse effects in cardiovascular system, MNPs have more therapeutic advantages. Herein, it's time to protect this ecosystem for better sustainable development in the new era of ocean economy, since MNPs are indeed huge, novel and promising biomedical resources for anti-infection of SARS-CoV-2 and its major variants as well as irCVD. The novel potential mechanisms may be through multiple targets and pathways regulating human immunity and inhibiting inflammation. In short, MNPs are worthy of translational research for further clinical application.

REVIEW ARTICLE

Marine natural products and human immunity: Novel biomedical resources for anti-infection of SARS-CoV-2 and related cardiovascular disease

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Running title: MNPs for SARS-CoV-2 & irCVD

ABSTRACT

Major marine natural products (MNPs) and marine organisms include sea urchin, sea squirts or ascidians, sea cucumbers, sea snake, sponge, soft coral, marine algae, and microalgae. As vital biomedical resources for the discovery of marine drugs, bioactive molecules, and agents for treatment of infectious diseases and major non-communicable diseases (mNCDs), these MNPs have bioactive potentials of antioxidant, anti-infection, anti-inflammatory, anticoagulant, anti-diabetic effects, cancer treatment, and improvement of human immunity. This article reviews MNPs as huge and novel biomedical resources for anti-infection of coronavirus, SARS-CoV-2 and its major variants (such as Delta and Omicron), as well tuberculosis, H. Pylori, and HIV infection, and as promising biomedical resources for infection related cardiovascular disease (irCVD), diabetes, and cancer. The anti-inflammatory mechanisms of current MNPs against SARS-CoV-2 infection are also involved. Moreover, since the use of other chemical agents for COVID-19 treatment are associated with some adverse effects in cardiovascular system, MNPs have more therapeutic advantages. Herein, it's time to protect this ecosystem for better sustainable development in the new era of ocean economy, since MNPs are indeed huge, novel and promising biomedical resources for anti-infection of SARS-CoV-2 and its major variants as well as irCVD. The novel potential mechanisms may be through multiple targets and pathways regulating human immunity and inhibiting inflammation. In short, MNPs are worthy of translational research for further clinical application.

KEYWORDS

anti-infection, cardiovascular disease, COVID-19, marine natural products, SARS-CoV-2

1 | INTRODUCTION

A comprehensive survey of deep coral reefs in the high seas showed that policymakers should give more attention to protection of ocean ecosystems and marine mammals [1, 2]. Due to a linkage with sources of sustainable food, energy, materials, biomedicine, and many others, it should be a priority attention from the United Nations for the future of this global ecosystem [3]. Currently, ocean economy is accelerating development in the globe and has become a vital support for human sustainable development. As important biomedical resources, drugs from marine organisms 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 marine compounds are also valuable tools in biomedicine and clinical applications [4, 5].

Major marine natural products (MNPs) and organisms include sea urchin, sea squirts or ascidians, sea cucumbers, sea snake, sponge, soft coral, marine algae, and microalgae. As vital biomedical resources for the discovery of marine drugs, bioactive molecules, and agents for treatment of infectious diseases and major non-communicable diseases (mNCDs), MNPs have many bioactive potentials. This article discusses the studies of MNPs as huge, novel, and promising biomedical resources for anti-infection of coronavirus (SARS-CoV-2 and its variants) and related cardiovascular disease (irCVD) as well as possible mechanisms linked to human immunity.

2 | MNPs: 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 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 (Table 1), including COVID-19 and acquired immunodeficiency syndrome (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 ($C_{14}H_{12}Br_2O_5$), 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 and the pregnane X receptor. Their novel agonists and antagonists can target human diseases, e.g., intestinal inflammation [13]. Marine invertebrate glycans (Sea squirts or 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 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 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 from the sea snake Hydrophis cyanocinctus, has potent both antimicrobial and anti-inflammatory activity by inhibiting the lipopolysaccharide (LPS)-induced production of nitric oxide (NO) and pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), Interleukin (IL)-1beta, 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 LPS (ligand of TLR4)-induced 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.

One of MNPs, marine cyanobacterium Lyngbya majuscule has a strong concentration-dependent anti-inflammatory activity by selectively inhibition the MyD88-dependent pathway [20]. 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 [21], could be used as new anti-inflammatory agents. Four drug candidates from novel bioactive sponge [22] can be used for treatment of not only inflammation but also cancer. Avarol is a marine sesquiterpenoid hydroquinone from the sponge with anti-inflammatory and antipsoriatic properties [23], it inhibits several key biomarkers up-regulated in the inflammatory response of psoriatic skin.

As bioactive molecules with the anti-inflammatory activity, microalgae-derived Oxylipins have the therapeutic potential in inflammatory diseases [24], could act as agonist of peroxisome proliferator-activated receptor gamma (PPAR-γ) and consequently inhibit nuclear factor-kappaB (NFκB) signaling pathway activation, thus lowering the production of inflammatory markers. The marine compound didemnin B decreases the activity of the cell types implicated in liver inflammation and fibrosis in vitro [25]. Other MNPs with anti-inflammatory effects include the extract of the marine sponge A. caissara [26], the sulfated galactan of the red marine alga Gelidium crinale [27], and the first marine invertebrate lectin, that is, holothuria grisea agglutinin [15]. But whether they have also antiviral effects, particularly anti-infection of SARS-CoV-2, it needs both experiments and trials to confirm their potentials.

3 | MNPs: NOVEL BIOMEDICAL RESOURCES FOR ANTI-INFECTION OF SARS-COV-2

As an enveloped RNA virus, coronavirus is a major cause of human respiratory diseases. The spike glyco-

protein (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 (Table 1), 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 [28]. Marine bacteria and fungi-derived bioactive 15 compounds showed promising potential roles against SARS-CoV-2 RNA dependent RNA polymerase and methyltransferase [29]. Some new MNPs compounds (bioactive peptides) isolated from marine organisms (such as vertebrates, invertebrates, seaweeds, or other sea microorganisms) have a role of prevention on SARS-CoV-2 infection due to potential angiotensin converting enzyme (ACE) inhibition and anti-hypertensive activities [30]. The most potent marine-derived metabolite from Red-Sea invertebrates, erylosides B [31], showed a great inhibitor activity against the SARS-CoV-2 M^{pro}.

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 [32]. A naturally existing sulfated polysaccharide, lmbda-carrageenan, 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 [33]. 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 [34]. As potential candidates of antiviral drug, marine sulfated polysaccharides can be used to prevent SARS-CoV-2 infection [35].

Carbohydrate-binding agents 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 [36]. Marine-derived natural metabolites from the soft coral [*Nephthea* sp.] can also be developed potential SARS-CoV-2 protease inhibitors [37]. 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 [38].

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 [39]. The nontoxic and non-immunogenic polyphosphate, a physiological, metabolic energy (ATP)-providing polymer, could possibly also exert a protective effect against SARS-CoV-2-cell attachment [40]. 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 and its major variants (Delta and Omicron). Hence, the MNPs and their derivatives could be a promising source of structurally diverse new anti-RNA virus therapeutics [41].

4 | MNPs: PROMISING BIOMEDICAL RESOURCES FOR IRCVD

Generally speaking, chronic or acute infection highly links to CVD (hypertension, myocardial infarction, arrhythmia, heart failure, and stroke), and other mNCDs, such as diabetes, cancer, respiratory and renal diseases, as well the related cardiovascular, diabetes, and cancer (CDC) strips [42, 43]. Here, the infection-related CVD is referred to as irCVD. Since MNPs have numerous health benefits, such as antioxidant, anti-infection, anti-inflammatory, anticoagulant, anti-diabetic effects, and cancer treatment [44, 45], they are not only suitable for treatment of infectious diseases, but also suitable for control and prevention irCVD and other mNCDs (Table 1).

In fact, MNPs derived compounds extracted from marine organisms are major sources of innovative medicine. And targeting lipid metabolism may treat related diseases [46]. Diphlorethohydroxycarmalol (DPHC) isolated from ishige okamurae (a brown algae) might be a potent inhibitor for alpha-glucosidase and alpha-amylase, which can alleviates postprandial hyperglycemia in diabetic mice [47]. Cytotoxic prodiginines isolated from marine bacteria have the antimelanoma effects by provoking cytostatic rather than cytotoxic

effects, cell cycle arrest at G0/G1 phase, induction of apoptosis and DNA damage, downregulation of survivin, and decreased clonogenic capacity in survivin knockdown cells [48].

Current studies showed that there are high associations between coronavirus (the SARS-CoV-2 and its variants) infection and CVD. As we known, cardiovascular health highly links to physical activity, nutrition, human immune status, and respiratory function, coronavirus can damage cardiovascular system by targeted respiratory and immune function [49]. On the one hand, COVID-9 may result in infection-related multi-organs failure in acute severe cases and mNCDs in the recovery cases, such as respiratory diseases, irCVD, and chronic kidney disease. On the other hand, as important risk factors for mortality, mNCDs are more strongly associated with outcomes and infection death in cases with COVID-19 [50].

Due to related vascular inflammation and direct vascular endothelial injury [51], SARS-CoV-2 infection may contribute to heart failure or other cardiovascular complications and multipleorgan failure. Heart failure in cases with COVID-19 involves in the abnormal activation of multiple inflammatory pathways [52]. Many studies found that a large number of cases with severe COVID-19 are easy to suffer from thrombotic complications in the venous and arterial systems. A report of an international panel showed that confirmed or suspected cases with COVID-19 infection have a high rate of acute ischemic stroke [53].

In fact, as a central feature of cases with SARS-CoV-2 infection, cerebrovascular events (stroke, ischemia, cerebrovascular injury, cerebral hemorrhage) often meet due to complement cascade, cytokine cascades, and endotheliopathy in the cerebral vasculature [54]. Thus, during the pandemic, there is an arising need of a more positive and intense thromboprophylaxis among cases hospitalized with COVID-19 due to asymptomatic deep vein thrombosis (DVT) [55].

Due to acute cardiac injury [56], cardiac arrhythmias [57, 58], major adverse cardiocerebrovascular events (MACCE) such as acute arterial events, a hypercoagulable status [59], and high mortality rate in cases with SARS-CoV-2 infection, better strategies are necessary to fight against COVID-19 and protect cardiovascular health. Hence, effective anti-infection of SARS-CoV-2 will help to protect cardiovascular system, reduce cardiac injury and cardiac arrest, and other irCVDs.

Since MNPs have a great potential role of anti-infection of SARS-CoV-2, they will also help to prevent irCVD. Some bioactive molecules extracted from marine organisms (vertebrates, invertebrates, seaweeds, or sea microorganisms) can be used not only to prevent SARS-Cov-2 infection but also to treat hypertension due to ACE inhibitory activity [30]. As one of MNPs with anticoagulant, thrombolytic, and fibrinolytic activities [60], seaweed has potential value for clinical use due to their natural origin, safety, and low cost. However, regardless of its anti-inflammatory and immunomodulatory properties, currently, no enough evidence to support the supposed favorable effects of statin (non-MNPs) therapy on COVID-19 outcomes [61].

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 [62]. Other studies found that MB-DSW has anti-diabetic and anti-obesity action [63] due to the stimulatory effect on mitochondrial biogenesis and function and enriched with Mg and Ca, and the effects on cholesterol metabolism [64] due to prevention of the high glucose- or FFA/glucose-induced increase of cellular cholesterol levels, and the role of the prevention of ultraviolet light-induced skin cancer development [65] 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 [66], 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. All in all, from anti-infection of coronavirus (the SARS-CoV-2 and its variants) to preventing irCVD, MNPs are huge biomedical resources, which is worthy of developing bio-agents.

5 | MECHANISMS LINKED TO HUMAN IMMUNITY AND FUTURE PROSPECTS

Totally, this is a new era of ocean economy since biomedicine and particularly AIDS [67] and COVID-

19 researches are indeed a growth industry (drug discoveries and vaccines development). The microbial flora, for example, K. pneumoniae HSL4 [68], 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 (Figure 1) [69]. 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] due to improvement of human immunity [70, 71].

However, marine radioactivity is a threat to human health or the environment [72]. Thus, ocean environment and marine microbes play strong roles in healthy ecosystems [73, 74]. Moreover, there are correlations between an ocean-atmosphere and human health [75], environmentally acquired infections and human disease [76, 77]. Hence, only healthy ocean & seas can meet human hope in the future. It's time to protect ocean ecosystem for human better sustainable development.

Global food and nutrition security is very important during COVID-19 [78], especially in low- and middle-income countries [79, 80]. Currently, there is an increasing risk of both obesity and undernutrition due to the COVID-19 pandemic [81]. And due to the challenge of malnutrition (undernutrition and overnutrition) [82, for example, having suboptimal intakes of seafood [83], as food lovers [84], we should improve nutrition status with effective strategies. Since there is an association between nutrition status and COVID-19 [85], we should assess positively the nutritional risks in COVID-19 cases with useful tools [86, 87], so as to promote nutritional care and the nutrition management in these patients [88]. As a healthy diet, seafood is an important choice. New business models will improve its development [89]. And by the online-to-offline food delivery [90] during the COVID-19 pandemic, people will combat effectively the SARS-CoV-2 and its major variants (Delta and Omicron).

Recent studies found that MNPs (both Brevenal and Chrysamide B) can reduce LPS induced cytokine/chemokine production and show their good performances of anti-inflammatory effects [91, 92]. The former can alter macrophage activation states and reduce inflammation in the lung, the latter has strong anti-inflammatory activity due to inhibition on the production of NO. The new potential mechanisms of MNPs against SARS-CoV-2 infection and COVID-19 may be through multiple targets and pathways regulating immunity and inhibiting inflammation. As innate immune cells, macrophage activation or dysregulated plays an important role in the hyperinflammatory response induced by SARS-CoV-2 infection [93].

As we all known, there are often cardiovascular-related conditions among patients with COVID-19 [94], such as myocarditis, acute myocardial infarction (AMI), and heart failure, that is, irCVD. Since the NACHT, leucine-rich repeat, and pyrin domain-containing protein 3 (NLRP3) inflammasome is responsible for the inflammatory response to injury or infection [95-97], whether MNPs can prevent the NLRP3 inflammasome activation or inhibit its formation in cardiomyocytes or not, it needs to further study. As we known, MNPs may not only lead to improvement in cancer induced complications but also reduce LPS-induced inflammation by the PI3K/Akt pathway due to anti-cancer and anti-inflammatory effects [98]. Since SARS-CoV-2 is prone to mutation as an RNA virus and its variants may gain resistance to available drugs or vaccines [99], hot pot of MNPs as a new cocktail therapy may reduce the chances of drug resistance due to multipathways targets so as to better protect human cardiovascular system.

As huge, novel, and promising biomedical resources, MNPs are highly expected becoming effective antiviral agents [100]. On the one hand, with the further understanding the pathogenesis of COVID-19 and the molecular mechanisms of SARS-CoV-2 infection and its variants, which involve in TLR2 signaling induced the production of proinflammatory cytokines (hyperactive cytokine release or a cytokine storm) [101], risk stratification of mild, moderate, severe COVID-19 for the acute and long-term adverse consequences [102], and human immunity [103, 104] and genetic mechanisms of critical illness [105], we can choose better clinical strategies by valuable models [106] to combat this severe viral disease.

On the other hand, due to the further understanding innate immunity and systems vaccinology [107], novel concepts and theories will help the vaccine development in this new platform and drug discoveries from these

MNPs. For example, recent mRNA vaccines can effectively protect subjects from infectious disease including SARS-CoV-2 infection [108], it's believed that we will combat finally the COVID-19 pandemic in the globe. Of course, just like convalescent plasma [109], clinical trials are needed to confirm the effects of these MNPs on fighting against COVID-19 and irCVD. In addition, better knowledge, attitudes, and practices [110] on the pandemic, such as incubation period [111], in-hospital mortality associated with T2D [112], vaccination effectiveness, and seasonal variations in incidence [113], are very helpful.

Currently, there are increasing threats from SARS-CoV-2 variants (114). With more understanding of epidemiological characteristics and pathogenicity of SARS-CoV-2 variants (115, 116), human immune responses (117-119) and neutralizing antibody response (120-122) during infection and vaccinations (123), and better rapid test (124) and precise diagnosis (125) of related variants, we can fight against these variants by various vaccines (126) and bispecific antibodies (127), and human immune memory, B-cells (128-130) and T cell immunity (131) by mRNA vaccines (132) or anti-Omicron antibody (133) will help to protect from infection of SARS-CoV-2 variants, and we can also predict future variants (134).

At the same time, machine learning-based models [135] are also very helpful to control the pandemic in the globe. Moreover, since the use of other chemical agents [136, 137] for COVID-19 treatment are associated with some adverse effects in cardiovascular system, MNPs have more therapeutic advantages. All in all, MNPs combined with these above effective strategies [138-140], such as development of a globally scalable diagnostic biomarkers and effective antiviral targets, discovery of specific protease inhibitors or other agents, such as Paxlovid [141, 142], Molnupiravir [143], a combination of BRII-196/BRII-198 [144], as well as healthy E(e)SEEDi lifestyle [70, 71] and better nutrient strategies [145-149], will help to combat the SARS-CoV-2 and its major variants (Delta and Omicron) [150-152], thus, combat the COVID-19 pandemic.

6 | CONCLUSION

As important biomedical resources for the discovery of marine drugs, bioactive molecules, and agents for treatment of infectious diseases and mNCDs, current MNPs have bioactive potentials of antioxidant, anti-infection, anti-inflammatory, anticoagulant, anti-diabetic effects, and cancer treatment by improvement of human immunity. They are not only huge and novel biomedical resources for anti-infection of the SARS-CoV-2 and its major variants (Delta and Omicron), but also promising biomedical resources for control and prevention of irCVD. Herein, it's time to protect this ecosystem for better sustainable development in the new era of ocean economy.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

C.H. contributed to manuscript conceptualization and design, literature review, figure production, manuscript writing and revised and approved the final version of the article.

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Figure 1 "Coronavirus (SARS-CoV-2 & Its Variants) Came, Marine Natural Products (MNPs) Halt".

Here, MA: marine (red) algae; Mi: microalgae; S: sponge; SC: sea cucumber and soft coral [*Nephthea* sp]; SSn: sea snake; SSq: sea squirt; SU: sea urchin; Sw: seaweed; SW: sea water; CoV: Coronavirus (SARS-CoV-2 & Its Variants). Whether a novel idea on "MNPs Hot Pot" will help to combat and prevent the COVID-19 pandemic, it's worthy of doing animal experimental studies and clinical trials.

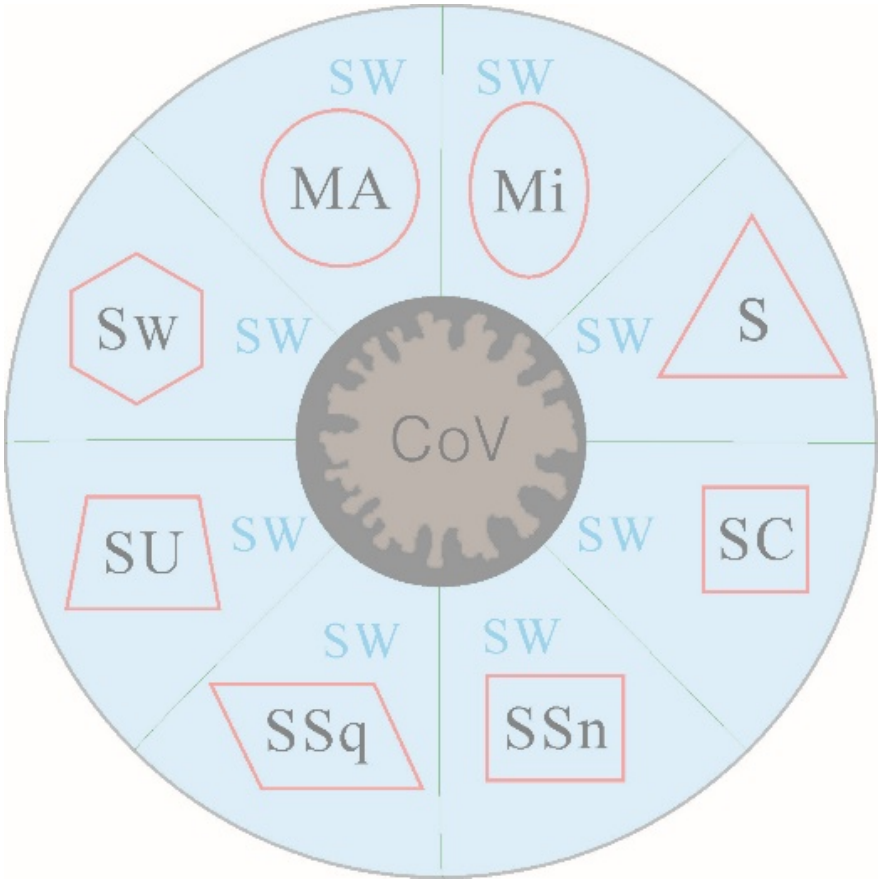

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Table 1.docx available at https://authorea.com/users/443069/articles/713597-marine-natural-products-and-human-immunity-novel-biomedical-resources-for-anti-infection-of-sars-cov-2-and-related-cardiovascular-disease