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MARINE-DERIVED COMPOUNDS FOR THE TREATMENT OF AUTOIMMUNE DISEASES

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Abstract
Their significance is highlighted by the chronicity, expense, and complexity of autoimmune diseases (Ads), which impact many organs and tissues. Addressing ads in patient populations calls for a more thorough strategy. An innovative method of obtaining an integrated therapeutic agent is through natural phytoconstituents. The marine environment is rich in a wide range of biomolecules with advantageous properties. Numerous substances that have been demonstrated to have immunomodulatory properties and may have therapeutic uses for Ads have been discovered in sponges, bacteria, fungi, cyanobacteria, and algae. It has been demonstrated that bioactive marine chemicals influence immunological processes and are essential for immunotherapies. The information regarding the particular effects of chemicals derived from marine organisms being used as food supplements or in the management of immune system diseases is increasing. In this paper, numerous sources of possible marine metabolic compounds like seagoing plants and animals are discussed. Following their isolation, characterization, and identification in recent years, a number of marine phytoconstituents are currently undergoing investigations for potential human use. In this review, we have attempted to compile data on phytoconstituents of marine origin that exhibit immunomodulatory and anti-inflammatory properties, and we have briefly examined their modes of action.
Keywords: Autoimmune disorders, phytoconstituents, marine, immunomodulatory

1. INTRODUCTION

Biomolecules produced from marine sources have drawn more attention as possible therapeutic targets for autoimmune diseases. Seas, straits, gulfs, bays, coves, and several islands encircle Nagasaki Prefecture, which has Japan's second-longest coastline after Hokkaido [1]. Biomolecules that are small to medium in size that have the ability to cross cell membranes and interfere with intracellular protein interactions, which causes autoinflammatory diseases such familial We have been developing a library of authentic marine microbial extracts, including Mediterranean fever. We have isolated more than 20,000 marine microbes[16]. In order to create shark nanobodies that may be used as novel therapeutic agents to treat autoimmune diseases, we have also been attempting to set up an indoor shark breeding facility. Sharks produce heavy-chain antibodies called immunoglobulin novel antigen receptors, which can bind a range of foreign antigens. These receptors contain five constant domains (CNAR) and one variable domain (VNAR). Escherichia coli produces a VNAR single-domain fragment known as a nanobody, which is the best treatment for autoimmune diseases[12].

Consequently, it is anticipated that shark nanobodies will resemble mammalian antibodies in terms of variety and affinity [3]. Shark nanobodies also have the potential to be used in the future to create highly precise, stable, efficient, and reasonably priced biotherapeutics because of their physical stability and low manufacturing costs. We give a brief overview of the history of the development of conventional small molecule drugs and monoclonal antibodies for the treatment of autoimmune diseases before introducing Nagasaki University's drug discovery system, which uses a novel marine microbial extract library and shark nanobodies. Both innate and adaptive immunity are components of the immune system. In addition to having cytotoxic activity against transformed and infected cells, innate immune cells, such as macrophages and dendritic cells, can also recognize pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides, flagellins, and double-stranded RNAs, and damage-associated molecular patterns (DAMPs, also known as danger signals or alarmins), which set off non-infectious inflammatory responses. Adaptive immune cells produce a wide variety of antigen-specific receptors on their cell surface or release antibodies as a result of gene recombination [19]. To reduce their symptoms, RA patients are offered immunosuppressive medications and anti-inflammatory biologics.

2. REVIEW OF LITERATURE

To develop treatments for inflammatory illnesses, novel methods for disrupting protein–protein interaction (PPI) in innate immunity cells are required, as PPI is essential for the cytoplasmic growth of inflammasomes. Here, we give a summary of how biologics and traditional small molecule medications have been developed to treat autoimmune diseases. In addition to joint pain, stiffness, and swelling, RA is an inflammatory and autoimmune disease that can cause fever, tiredness, and exhaustion. Rheumatic pain was one of the most excruciating symptoms to be relieved during the thousands of years that people have had RA[5].

Some plant or herb extracts or decoctions, such as poplar bark, meadowsweet flower (Spirea), and willow tree bark (Salix), may have contained salicylates. In ancient Greece, Hippocrates recommended using willow tree bark to treat fever and rheumatic discomfort. The first clinical report on the use of willow bark treatments to treat fever and pain was published in 1763. Glucose and salicylic alcohol can be produced by hydrolysing salicin, an alcoholic β-glucoside prodrug. Salicylic acid, a molecule having pharmacological activity, is produced by further metabolism of salicylic alcohol. Salicylaldehyde from meadowsweet and salicin from willow bark were used to create pure salicylic acid in 1835–1838 [14].

Because of its toxicity and bitterness, which can result in nausea, vomiting, and stomach discomfort in addition to hearing issues, acetylsalicylic acid was more effective than salicylic acid as a treatment for rheumatic disorders. By refining the production pathway to acetylsalicylic acid, Felix Hoffmann created an acceptable profile and decreased the toxicity of the derivative in 1897. The most often used medication throughout the previous century was acetylsalicylic acid, which is currently marketed under the name. The drug is also used clinically to treat RA patients, albeit it is unknown exactly what mechanism underlies its anti-rheumatic action. Nevertheless, it has been shown that hydroxychloroquine prevents the production of activated immune effector cells and pro-inflammatory cytokines.

3. MATERIALS AND METHOD

Most physiological functions are inhibited by conventional NSAIDs because they block both COX-1 and COX-2, which might result in adverse effects such gastrointestinal toxicities. In order to create treatments that are specific for inflammatory tissues, selective inhibitors of COX-2 were evaluated, modified, and manufactured after this finding. Celecoxib, etoricoxib, parecoxib, and valdecoxib are a few examples of COX-2 selective inhibitors, as shown in Supplementary Fig. The empirical discovery of NSAIDs led to the discovery of glucocorticoids, which were found to have therapeutic effects on RA in both pregnancy and jaundice. These clinical data led to the hypothesis that a factor produced by the adrenal cortices would be able to alleviate the symptoms of rheumatic illnesses. A class of steroid hormones known as glucocorticoids regulates glucose metabolism by binding to the glucocorticoid receptor [7].

The liver enzyme can break down the prodrug prednisone to produce the pharmacologic drug prednisolone. Even though glucocorticoids are especially effective in treating rheumatic illnesses, long-term use of these drugs is not recommended for RA because of the possibility of adverse side effects such infection, gastrointestinal irritation, and bone damage. Glucocorticoids are mostly used to treat rheumatic disorders by inhibiting the immune system. The effects of methotrexate on RA and psoriatic arthritis were investigated in the 1960s since it has been demonstrated to compromise the immune system. As anticipated, methotrexate lessened the symptoms of the diseases. Additionally, the drug may be administered for a longer duration than glucocorticoids.

As a paradigm for disease-modifying anti-rheumatic medications (DMARDs), methotrexate decreases pro-inflammatory cytokines and immune effector cells by blocking dihydrofolate reductase, which is necessary for DNA and RNA synthesis. Since many inhibitors depress the immune system, which negatively affects the proliferation and activity of rapidly proliferating cells like lymphocytes, they were studied to see if they may be utilized as DMARDs in the treatment of rheumatic disorders. An isoxazole derivative called leflunomide prevents

the dihydroorotate dehydrogenase from catalysing the conversion of dihydroorotate to orotate and the transfer of electrons from quinone to quinol. This mechanism is essential to the electron transfer chain and pyrimidine production. An aminoquinoline derivative with anti-malarial and immune-modulating properties is hydroxychloroquine. Cyclophosphamide is an alkylating medication used to treat cancer. The medication can be used to treat autoimmune diseases since it suppresses immune responses. Cyclophosphamide is used for severe autoimmune illnesses when traditional DMARDs are ineffective due to its possible toxicity[18].
After being digested, sulfasalazine is absorbed in the gut as amino salicylic acid and sulphapyridine. The drug's precise mechanism is yet unknown, although one possible explanation is that it inhibits prostaglandin formation, which reduces inflammation. Additionally, it was hypothesized that the medication suppresses the immune system's effector cells by blocking enzymes that need folate. As a calcineurin inhibitor, cyclosporine impairs effector T cell activity and suppresses the generation of pro-inflammatory cytokines. On the other hand, tiny compounds typically have a difficult time disrupting PPI, whereas conventional synthesized medications can be ingested into the cells. As a result, creating mid-sized molecules or molecularly engineered nanobodies is essential for creating next-generation medications that treat autoimmune diseases like FMF and Still's disease. To develop mid-size medicines and conventional small-size compounds, we have been isolating sea microorganisms and establishing an authentic marine microbial extract library in our lab at Nagasaki University.

4. RESULT AND DISCUSSION

The oceans are extremely diverse because they currently make up 99% of all living space and around three-fourths of the Earth's surface. Marine bacteria are the source of much of the genetic and metabolic variability of life, with a population of over 3.6 × 1029 and an aggregate cellular carbon content of 3 × 1017 g. Consequently, a wide range of biological processes can be initiated by the action of several natural products on a variety of biomolecules, including enzymes and receptors. The most crucial stage in the creation of new medicines is identifying unique backbone structures for chemicals or biomolecules. Therefore, original drug libraries with a range of molecular weights and chemical spaces must be used[10].

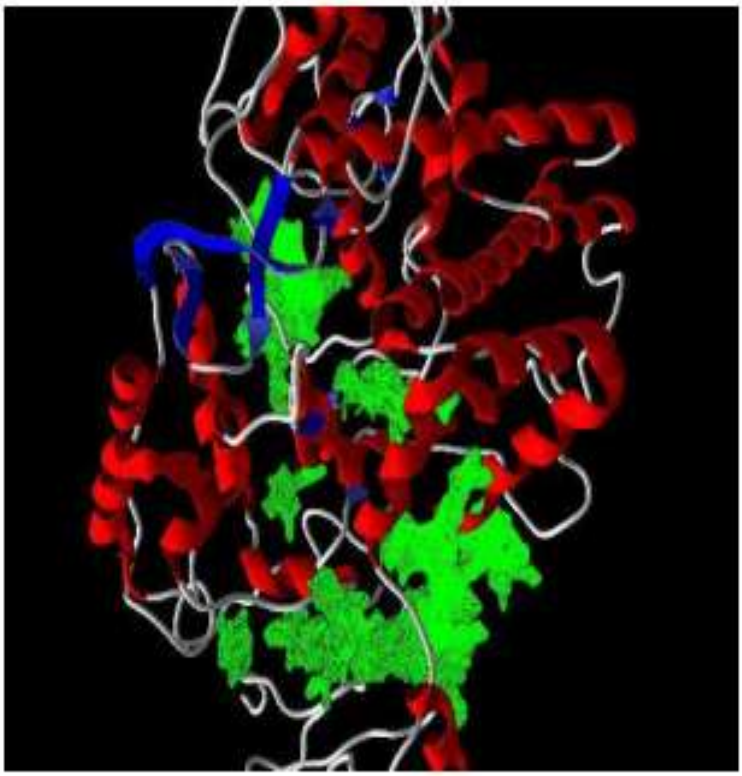

Figure 1: Predicted binding sites

Natural substances have contributed significantly to therapeutic leads throughout the last four decades. A comprehensive examination of FDA-approved pharmaceuticals submitted between January 1981 and September 2019 found that natural products are intimately related to 49.2% of all medications. Of them, 3.8% are unaltered natural goods, 0.8% are plant-based medications, 18.9% are natural product derivatives, 3.2% are synthetic medications that mimic natural products, and 22.5% are natural product mimetics[14].

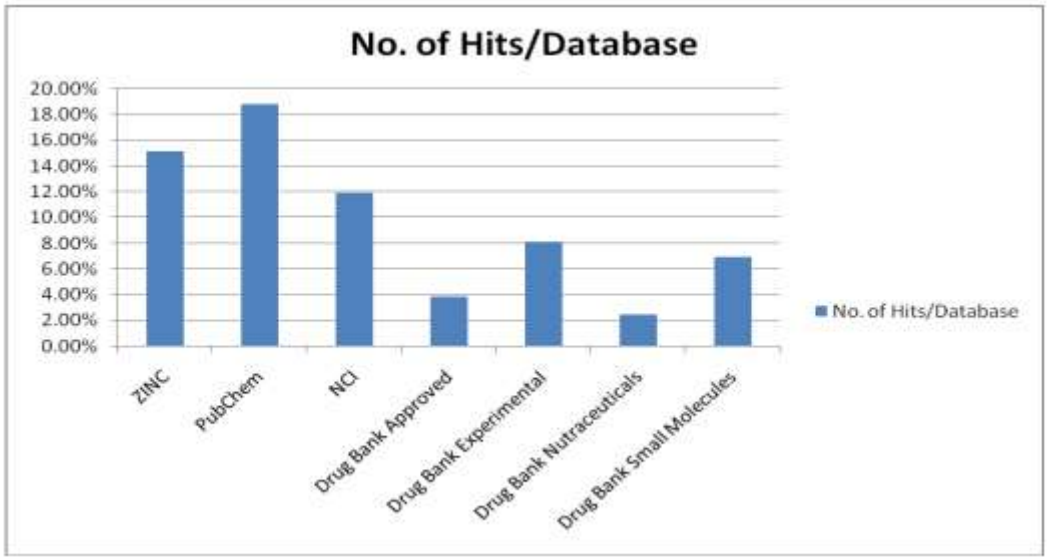

Figure 2: Percentage of hits with better binding energy scores

The majority of medications used to be human-accessible plant and herb extracts or decoctions. The methodical gathering of marine microorganisms and the production of marine microbial extract libraries have been made possible by the development of marine microbe culture systems and identification methods. The most important stage in the creation of medications is identifying novel chemical or biomolecule backbone structures.

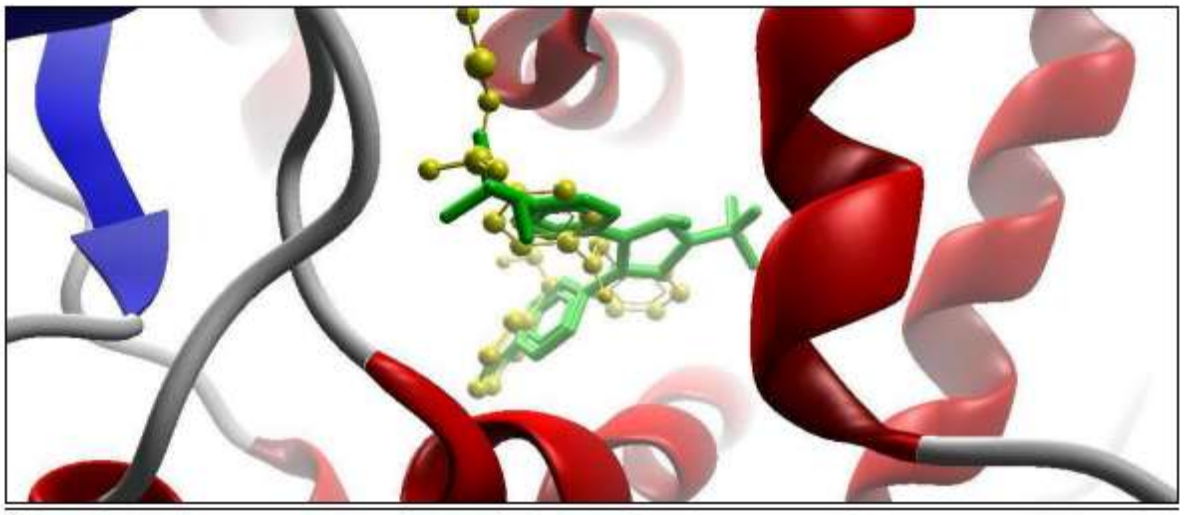

Figure 3: Binding modes of SC-558

We set out to isolate marine microorganisms from the beaches of Nagasaki Prefecture in order to efficiently gather them. Due to the low effectiveness of microbial colony growth, our initial attempts to separate marine microorganisms from saltwater failed. As a result, we mostly separated marine microorganisms and collected marine creatures from the alimentary canal. As mentioned before, the majority of marine life, including sea urchins, crabs, lobsters, sea cucumbers, sea anemones, oysters, and shrimp, was harvested from the coasts. After being streaked onto seawater and marine agar plates, the alimentary canal samples were cultured for a few days at 26 °C.

5. CONCLUSION

The pharmacological targets of conventional small-molecule medications and biologics are frequently intracellular enzymes or receptors that detect small-molecule substrates or ligands, membrane-bound receptors, or extracellular proteinaceous factors. However, in situations of autoinflammatory diseases like FMF, intracellular PPI, such as the pyrin-ASC interaction, should be considered as a therapeutic target. A new class of targets necessitates a new class of therapies. If this is accurate, then the characteristics of shark nanobodies make them suitable for use as intracellular PPI inhibitors. We anticipate that individuals with autoimmune diseases may benefit therapeutically from shark nanobodies. Shark nanobodies, like camelid nanobodies, have a strong

structural composition because the CDR loops are maintained by intra-loop disulfide and hydrogen bonds and several charged and hydrophilic side chains of charged amino acids are exposed at the surface of the Ig scaffold.

REFERENCES

- Bilal, Muhammad, Maimoona Qindeel, Leonardo Vieira Nunes, Marco ThúlioSaviatto Duarte, Luiz Fernando Romanholo Ferreira, Renato Nery Soriano, and Hafiz MN Iqbal. "Marine-derived biologically active compounds for the potential treatment of rheumatoid arthritis." *Marine Drugs* 19, no. 1 (2020): 10.
- Shin, S. J., Park, Y., & Shin, S. U. (2024). Decentralized Fair Data Trading Scheme based on mCL-ME Primitive. *Journal of Internet Services and Information Security, 14*(4), 569-589. https://doi.org/10.58346/JISIS.2024.I4.036
- Reginald, P. J. (2025). Design of an Intelligent V2G Energy Management System with Battery-Aware Bidirectional Converter Control. National Journal of Intelligent Power Systems and Technology, 1(1), 12-20.
- Rawat, Ekta, Suman Sharma, Pragya Sharma, and Qumar Negar. "Marine Metabolites Targeting Inflammatory and Autoimmune Diseases." (2025).
- Turan, C., Yağlıoğlu, D., Doğdu, S. A., Gürlek, M., Ergüden, D., Ivanova, P. P., & Raykov, V. S. (2023). Existence of Belone svetovidovi Collette & Parin, 1970 in the Marmara Sea and Black Sea Coasts of Türkiye. *Natural and Engineering Sciences*, *8*(2), 72-81. http://doi.org/10.28978/nesciences.1331296
- Prasath, C. A. (2025). Green Hydrogen Production via Offshore Wind Electrolysis: Techno-Economic Perspectives. National Journal of Renewable Energy Systems and Innovation, 8-17.
- Montuori, Eleonora, Donatella de Pascale, and Chiara Lauritano. "Recent discoveries on marine organism immunomodulatory activities." *Marine Drugs* 20, no. 7 (2022): 422.
- Akrami, R., Chitsaz, H., & Ahmadi, Z. (2024). Effect of dietary dehydrated sour lemon peel (Citrus limon) powder on metabolic enzymes, serum biochemistry and stress status of rainbow trout (Oncorhynchus mykiss) juvenile. *International Journal of Aquatic Research and Environmental Studies*, *4*(1), 91-99. http://doi.org/10.70102/IJARES/V4I1/8
- Al-Hussaniy, Hany A., Sammar Jassim Mahan, Zainab Mohamed Redha, Ahmed Hameed AlSaeedi, Ali Majeed Ali Almukram, Amjad I. Oraibi, Mostafa Adnan Abdalrahman et al. "Marine-derived bioactive molecules as modulators of immune pathways: A molecular insight into pharmacological potential." *Pharmacia* 72 (2025): 1-10.
- Joshi, P., & Singh, K. (2024). Strength of Materials: Analysis and Design of Mechanical Components. *Association Journal of Interdisciplinary Technics in Engineering Mechanics*, *2*(4), 1-5.
- Zhang, Tao, Zijun Ouyang, Yueran Zhang, Haiyan Sun, Lingdong Kong, Qiang Xu, Jiao Qu, and Yang Sun. "Marine Natural Products in Inflammation-Related Diseases: Opportunities and Challenges." *Medicinal Research Reviews* (2025).
- Kumar, T. S. (2025). A Comparative Study of DTC and FOC Techniques in Multiphase Synchronous Reluctance Drives. National Journal of Electric Drives and Control Systems, 1(1), 12-22.
- Nazarova, J., &Bobomuratov, T. (2023). Evaluating the Clinical Utility of Genetic Testing in Guiding Medication Selection. *Clinical Journal for Medicine, Health and Pharmacy*, *1*(1), 64-72.
- Meenakshi, Dhanalekshmi U., Gurpreet Kaur Narde, Sameera Siddiqui, and Alka Ahuja. "Marine bioactive phytoconstituents in autoimmune disorders: role and mechanism-A review." *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistryrrent Medicinal Chemistry-Anti-Inflammatory and Anti-Allergy Agents)* 22, no. 1 (2023): 10-29.
- Carter, E., & Tanaka, H. (2024). Harmonizing Medical Terminology across Multilingual Healthcare Systems: A Global Framework. *Global Journal of Medical Terminology Research and Informatics*, *2*(1), 8-12
- Abdullah, D. (2025). Comparative Analysis of SIC and GAN-Based Power Converters in Renewable Energy Systems. National Journal of Electrical Machines & Power Conversion, 11-20.
- Al-Hussaniy, Hany A., Sammar Jassim Mahan, Zainab Mohamed Redha, Ahmed Hameed AlSaeedi, Ali Majeed Ali Almukram, Amjad I. Oraibi, Mostafa Adnan Abdalrahman et al. "Marine-derived bioactive molecules as modulators of immune pathways: A molecular insight into pharmacological potential." *Pharmacia* 72 (2025): 1-10.
- Baggyalakshmi, N., Mohana Dhanushiya, A. S., & Revathi, R. (2023). Streamlined Yearbook Automation System. *International Academic Journal of Innovative Research*, *10*(2), 56–64. https://doi.org/10.9756/IAJIR/V10I2/IAJIR1009
- Anh, D. L. (2025). Literature Review of Management Accounting Practice in Vietnam from 2010 TO 2024. Calitatea, 26(204), 42-56.
- Senthilkumar, Kalimuthu, and Se-Kwon Kim. "Marine invertebrate natural products for anti-inflammatory and chronic diseases." *Evidence-Based Complementary and Alternative Medicine* 2013, no. 1 (2013): 572859.

- Bhaskaraprasath, S. K., Manibharathi, J., Poovarasan, G., Vignesh, C., & Nagarajan, G. (2023). Automated Bird Species Identification using Audio Signal Processing. *International Journal of Advances in Engineering and Emerging Technology*, *14*(1), 133–136
- Surendar, A. (2025). Model Predictive Control of Bidirectional Converters in Grid-Interactive Battery Systems. Transactions on Power Electronics and Renewable Energy Systems, 13-20.
- Moorthy, Narayana Subbiah Hari Narayana, VijayakumariPratheepa, and Elangovan Manivannan. "Natural product derived drugs for immunological and inflammatory diseases." In *Natural Products in Clinical Trials: Volume 1*, pp. 31-78. Bentham Science Publishers, 2018
- Verma, A., & Mehta, N. (2024). The Role of IoT in Modern Electrical Systems: An Interdisciplinary Approach in the Periodic Series. In *Smart Grid Integration* (pp. 13-18). Periodic Series in Multidisciplinary Studies.
- Abdullah, D. (2025). Redox Flow Batteries for Long-Duration Energy Storage: Challenges and Emerging Solutions. Transactions on Energy Storage Systems and Innovation, 1(1), 9-16.
- Tanaka, Yoshimasa, Megumi Nishikawa, Kaho Kamisaki, Saki Hachiya, Moeka Nakamura, Takahiro Kuwazuru, Susumu Tanimura, Kiyoshi Soyano, and Kohsuke Takeda. "Marine-derived microbes and molecules for drug discovery." *Inflammation and Regeneration* 42, no. 1 (2022): 18.