WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Comprehensive Review on Marine Drugs

Sreelakshmi K P *[a], Archana S [b], Saranya S P [c]

[a] ***Assistant professor Department of Pharmacognosy, Nehru College of Pharmacy, Pampady, Thiruvilwamala, Thrissur, Kerala-680588***
[b] **M Pharm student** ***Department of Pharmacognosy, Nehru College of Pharmacy, Pampady, Thiruvilwamala, Thrissur, Kerala-680588***
[C] **M Pharm student** ***Department of Pharmacognosy, Nehru College of Pharmacy, Pampady, Thiruvilwamala, Thrissur, Kerala-680588***

A B S T R A C T

Marine microorganisms have received much attention in biological discoveries due to the special physicochemical characteristics they have acquired as they have adapted to the extreme conditions present in the marine environment. Unique marine microorganisms and their biologically active metabolites have been noted as potential sources for use as sustainable food and pharmaceutical ingredients. Marine organisms have excellent potential against several diseases due to the natural biomedical compounds present in them. So that the marine environment is most utilized and trusted for drugs with therapeutic uses, bioactive compounds, etc. Marine drugs have diverse structural features and mechanisms of action. They are known for antibiotic, antiviral, anti-inflammatory, anticancer, anti-fungal, anti-obesity, and Immuno-protective activities. Marine medicine is also used for heparin overdose, vaccine carriers, and omega-3 fatty acid supplementation in the diet. In the present manuscript, we have thoroughly studied marine drugs that have been successfully used in the clinic.

Keywords: Trabectedin, Ziconotide, Brentuximab vedotin, Tetrodotoxin, Plitidepsin

INTRODUCTION

Oceans occupy more than 70% of the planet's surface, and they are home to 95% of the biosphere. The first living things in the sea originally arose more than 3500 million years ago. Since their significance to human life has come to light more and more recently, so has our interest in understanding how marine ecosystems work. Over the course of evolution, marine bacteria have changed the chemistry of the seas and atmosphere. In marine habitats, there are thousands of different species of bacteria, fungus, and viruses that construct intricate microbial food webs.

The marine flora and animals are an important source of novel molecular entities. There are approximately 5 million species in about 30 phyla in the waters of the planet. Terpenes, polyketides, and other chemical classes are among those found in marine natural products.

In this review, we present drugs from marine compounds, it's biological source, purification process and therapeutic action of the particular microorganisms.

1.Trabectedin

1.1.Biological source:

Trabectedin is a synthetic anticancer drug that was initially derived from a natural product found in marine organisms. It was first isolated from the marine tunicate Ecteinascidia turbinata, also known as the Caribbean sea squirt. Tunicates are marine invertebrates commonly found in oceans around the world.

1.2 Purification:

Trabectedin is an anticancer drug derived from a marine organism called Ecteinascidia turbinate, also known as the sea squirt. The process of purifying trabectedin involves several steps. Here is a general outline of the purification process:

Collection and extraction: Ecteinascidia turbinate is collected from its natural habitat, typically in the ocean. The organisms are then carefully processed to extract the active compound, trabectedin.

Filtration: The crude extract obtained from the marine organism is typically subjected to filtration to remove any solid impurities, such as cellular debris or other particulate matter.

Solvent extraction: Trabectedin is often present in the extract as a mixture with other compounds. Solvent extraction techniques, such as liquid-liquid extraction, are employed to separate trabectedin from these impurities. Selective solvents are used to partition trabectedin into the desired solvent phase.

Purification by chromatography: Various chromatographic techniques, such as column chromatography or preparative high-performance liquid chromatography (HPLC), can be used to further purify the trabectedin compound. These techniques exploit the differences in chemical properties, such as polarity or molecular weight, to separate the target compound from other impurities.

Crystallization: After chromatographic purification, the trabectedin compound can be further purified through crystallization. Controlled precipitation or cooling of a solvent system can lead to the formation of pure trabectedin crystals, which can then be collected and washed to remove residual impurities.

Drying and formulation: The purified trabectedin is typically dried to remove any residual solvents, resulting in a solid form of the drug. It can then be formulated into the desired pharmaceutical product, such as capsules or injectable formulations.

1.3 Therapeutic uses

Soft Tissue Sarcoma: Trabectedin is approved for the treatment of advanced soft tissue sarcoma (STS) in patients who have already received prior chemotherapy, including anthracyclines and ifosfamide, and have shown disease progression. Soft tissue sarcomas that Trabectedin may be used for include liposarcoma and leiomyosarcoma.

Ovarian Cancer: Trabectedin is approved for the treatment of recurrent, platinum-sensitive ovarian cancer. It is used in combination with pegylated liposomal doxorubicin (PLD) for patients who have relapsed after previous platinum-based chemotherapy. This combination is used in cases where other treatment options have been exhausted or are not suitable.

It's important to note that Trabectedin is typically administered by a healthcare professional in a clinical setting due to its specialized administration requirements and potential side effects. The specific dosage, treatment regimen, and duration of therapy may vary based on the individual patient's condition and the judgment of the treating physician.

2. Ziconotide

2.1 Biological source:

The biological source of ziconotide is the venom of a species of marine cone snail called Conus magus. Cone snails are predatory marine snails that live in tropical and subtropical waters around the world. They produce a complex venom that contains a variety of bioactive compounds, including peptides.

2.2 Purification:

The purification process of ziconotide involves isolating and purifying the desired compound from the venom of the cone snail. Here is a general outline of the purification steps:

Venom Extraction: The venom of the cone snail is collected through a process known as milking. The snail is gently stimulated, causing it to release its venom, which is then collected.

Venom Fractionation: The collected venom is typically a complex mixture containing numerous bioactive compounds. To isolate ziconotide, the venom undergoes fractionation, which involves separating the venom into different fractions based on their properties (e.g., size, charge, hydrophobicity).

Chromatography: Chromatographic techniques are commonly used for the purification of ziconotide. This involves passing the venom fractions through a chromatography column packed with a stationary phase. Different compounds in the venom interact differently with the stationary phase, allowing for their separation. Various types of chromatography, such as reversed-phase chromatography or ion exchange chromatography, may be employed.

Analytical Techniques: Throughout the purification process, analytical techniques like high-performance liquid chromatography (HPLC) and mass spectrometry (MS) are used to monitor the separation and purity of ziconotide. These techniques help ensure that the desired compound is being isolated and that impurities are removed.

Refinement and Concentration: The isolated ziconotide fraction is further refined and concentrated to increase its purity and potency. This can involve additional chromatography steps or other purification methods, depending on the specific requirements.

Formulation: Once the purified ziconotide is obtained, it is typically formulated into a suitable pharmaceutical preparation, such as a solution for intrathecal administration, which is the common route of delivery for ziconotide.

2.3 Therapeutic uses:

Chronic Pain: Ziconotide is primarily used for the management of severe chronic pain, such as cancer-related pain, neuropathic pain, and severe chronic back pain. It is typically reserved for patients who have not achieved adequate pain relief with other analgesics or who cannot tolerate other medications due to side effects.

Failed Back Surgery Syndrome: Failed Back Surgery Syndrome (FBSS) refers to persistent or recurrent pain following back surgery. Ziconotide can be considered as a treatment option for patients with FBSS who have not responded well to other therapies.

Neuropathic Pain: Ziconotide has shown effectiveness in managing neuropathic pain, which is caused by damage or dysfunction of the nervous system. It may be used in conditions such as diabetic neuropathy, post-herpetic neuralgia, and complex regional pain syndrome.

Cancer Pain: Ziconotide can be used as an adjunctive treatment for severe cancer-related pain that is not adequately controlled with other analgesics. It may provide relief and improve the quality of life in cancer patients with refractory pain.

3. Brentuximab vedotin

3.1 Bilogical source:

Brentuximab is produced using recombinant DNA technology, where the gene encoding the antibody is inserted into a host cell, typically Chinese hamster ovary (CHO) cells. These modified cells are then grown in bioreactors, allowing them to produce the antibody in large quantities. The antibody is purified from the cell culture and then chemically linked to a potent anti-cancer drug called monomethyl auristatin E (MMAE), forming the antibody-drug conjugate.

3.2 Purification:

The purification process for Brentuximab vedotin involves several steps to obtain a highly purified and concentrated form of the antibody-drug conjugate. Here is a general overview of the purification process:

1. Cell culture harvest: The host cells (such as CHO cells) that have been genetically modified to produce the antibody are cultured in bioreactors. Once the cells have grown and produced the antibody, the cell culture is harvested.
2. Clarification: The harvested cell culture is first subjected to a clarification step to remove cellular debris, cell fragments, and other solid impurities. This can be achieved through techniques such as centrifugation or filtration.
3. Protein A affinity chromatography: The next step is the purification of the antibody using Protein A affinity chromatography. Protein A is a ligand that specifically binds to the Fc region of antibodies, allowing for selective purification. The cell culture supernatant containing the antibody is passed through a column containing immobilized Protein A. The antibody binds to Protein A while impurities are washed away. The antibody is then eluted from the column, typically using a low-pH buffer or other suitable elution conditions.
4. Viral clearance: To ensure product safety, viral clearance steps are implemented. This may involve techniques such as filtration or inactivation methods to remove or inactivate any potential viral contaminants.
5. Concentration and diafiltration: The purified antibody is concentrated and the buffer is exchanged using ultrafiltration and diafiltration techniques. This step helps to remove low molecular weight impurities and adjust the final formulation of the antibody-drug conjugate.
6. Formulation and final filtration: The concentrated antibody-drug conjugate is formulated with suitable buffers and excipients to ensure stability and patient safety. The final formulation is then subjected to a sterile filtration step to remove any remaining particles or microorganisms.

After the purification process is completed, the Brentuximab vedotin is typically filled into vials or other suitable containers, labeled, and packaged for distribution and use in clinical settings.

3.3 Therapeutic uses:

- Hodgkin lymphoma: Brentuximab vedotin is indicated for the treatment of classical Hodgkin lymphoma (cHL) in several settings. It is used as a first-line treatment in combination with chemotherapy for stage III or IV cHL patients who are not suitable for a stem cell transplant. It is also used as a consolidation treatment after autologous stem cell transplantation (ASCT) or as a salvage treatment for relapsed or refractory cHL.
- Systemic anaplastic large cell lymphoma (sALCL): Brentuximab vedotin is approved for the treatment of CD30-positive sALCL, including primary cutaneous ALCL or ALK-positive and ALK-negative ALCL. It is used as a frontline treatment in combination with chemotherapy or as a standalone treatment for relapsed or refractory sALCL after other systemic therapies have been tried.
- Primary mediastinal large B-cell lymphoma (PMBCL): Brentuximab vedotin is indicated for the treatment of PMBCL in patients who are not eligible for ASCT or after failure of two or more prior multi-agent chemotherapy regimens.
- Cutaneous T-cell lymphoma (CTCL): Brentuximab vedotin is used in the treatment of CD30-positive CTCL after failure of one or more prior systemic therapies.

4.Tetrodotoxin

4.1 Biolodical source:

The biological source of tetrodotoxin is primarily associated with various marine animals, although it can also be found in some terrestrial organisms. Some notable marine sources of tetrodotoxin include:

1. Pufferfish: Pufferfish, also known as blowfish or fugu, are the most well-known source of tetrodotoxin. The toxin is produced in the ovaries, liver, intestines, and skin of certain pufferfish species, acting as a defense mechanism against predators. Pufferfish consumption is regulated and highly controlled due to the toxicity of tetrodotoxin.
2. Blue-ringed octopus: The blue-ringed octopus, found in the waters of the Pacific and Indian Oceans, carries tetrodotoxin in its saliva. The toxin is used for hunting and defense purposes by this small but highly venomous octopus species.
3. Nudibranchs: Some species of colorful sea slugs known as nudibranchs have been found to possess tetrodotoxin. These marine mollusks acquire the toxin by feeding on organisms such as sponges or other invertebrates that produce tetrodotoxin.
4. Various marine invertebrates: Tetrodotoxin has also been detected in other marine invertebrates, including certain species of starfish, sea anemones, crabs, and worms. The toxin in these organisms is thought to be acquired through the consumption of toxin-producing bacteria or other sources

4.2 Purification:

The purification of tetrodotoxin (TTX) from its biological sources is a challenging process due to its high toxicity and low concentrations in the organisms. Here is a general overview of the purification steps involved:

Extraction: The first step involves the extraction of tetrodotoxin from the biological source. This typically involves homogenizing or macerating the tissues of the organism and extracting the toxin using suitable solvents. Depending on the source, different extraction methods may be employed.

Filtration: The extract is usually subjected to filtration to remove solid particles and debris, obtaining a clarified solution.

Concentration: The clarified extract is then concentrated to reduce its volume and increase the relative concentration of tetrodotoxin. This can be done through various techniques such as solvent evaporation, vacuum distillation, or solid-phase extraction.

Chromatographic separation: Chromatography techniques, such as high-performance liquid chromatography (HPLC), are commonly employed for the purification of tetrodotoxin. These methods exploit the differences in chemical properties and interactions of the toxin with the stationary and mobile phases to separate it from other compounds present in the extract.

Fractionation and purification: Further fractionation steps may be employed to isolate tetrodotoxin from other components present in the extract. This can involve additional chromatographic techniques or other separation methods based on the specific properties of the toxin.

Analysis and quality control: Throughout the purification process, the obtained fractions or purified tetrodotoxin are analyzed using analytical techniques such as mass spectrometry or nuclear magnetic resonance spectroscopy to confirm the identity and purity of the toxin.

4.3 Therapeutic uses:

Tetrodotoxin (TTX) is a potent neurotoxin and is not used for therapeutic purposes in humans. In fact, tetrodotoxin is considered one of the most potent natural toxins known. It acts by blocking voltage-gated sodium channels, resulting in the inhibition of nerve impulses and leading to paralysis and potentially fatal respiratory failure if consumed in high amounts.

While tetrodotoxin has no approved therapeutic uses in humans, it has been studied for its potential applications in scientific research and medicine. Some of these areas of study include:

1. Neuroscience research: Tetrodotoxin is often used in neuroscience laboratories to study the function of voltage-gated sodium channels and their role in nerve conduction. Researchers use tetrodotoxin to selectively block sodium channels and investigate their contributions to various physiological processes.
2. Pain research: The blockade of sodium channels by tetrodotoxin has led to its use in studying pain mechanisms. By selectively inhibiting the activity of sensory neurons, researchers can better understand the underlying mechanisms of pain and develop potential treatments.
3. Local anesthesia: Tetrodotoxin has been investigated as a potential local anesthetic due to its ability to block nerve impulses. However, its extreme potency and potential for toxicity have limited its practical application in this area.
4. Biomedical engineering: Tetrodotoxin has been utilized in the development of biosensors and bioanalytical devices for detecting and monitoring sodium channel activity. These technologies have potential applications in diagnostics and drug discovery.

5. Plitidepsin

5.1 Biological source:

Plitidepsin, also known by its brand name Aplidin, is a pharmaceutical drug that has been derived from a marine source. Specifically, it is obtained from a marine organism called Aplidium albicans, which is a type of tunicate or sea squirt. Aplidium albicans is a sessile filter-feeding invertebrate that belongs to the family Polyclinidae.

5.2 Purification:

The purification of plitidepsin involves several steps to isolate the compound from the extract obtained from Aplidium albicans. Here is a general overview of the purification process:

Collection and preparation of the source material: Aplidium albicans organisms are collected from their natural habitat, typically from coastal regions where they are abundant. The collected organisms are cleaned and processed to remove any debris or unwanted materials.

Extraction: The tissues of Aplidium albicans are homogenized or mechanically disrupted to release the bioactive compounds, including plitidepsin. This step often involves grinding or blending the organisms with a suitable solvent or extraction buffer to facilitate the extraction process.

Filtration and centrifugation: The extract obtained from the previous step may contain solid particles or cellular debris. Filtration techniques such as vacuum filtration or centrifugation are employed to remove these impurities, resulting in a clearer solution.

Chromatographic separation: Chromatography is a widely used technique in drug purification. Various chromatographic methods, such as high-performance liquid chromatography (HPLC), are employed to separate plitidepsin from other compounds present in the extract. HPLC is particularly effective in separating compounds based on their chemical properties, such as polarity and molecular weight.

Fractionation: Once plitidepsin is separated from other compounds, further fractionation steps may be performed to isolate the pure compound. Fractionation techniques like preparative HPLC or column chromatography can be employed to separate plitidepsin from closely related compounds.

Characterization and quality control: The isolated plitidepsin is subjected to various analytical techniques to confirm its purity, identity, and potency. These techniques may include mass spectrometry, nuclear magnetic resonance (NMR) spectroscopy, and other biochemical assays. The compound's physical and chemical properties are also evaluated during this stage.

Formulation and packaging: After purification and characterization, the plitidepsin is typically formulated into a suitable pharmaceutical product, such as a solution or lyophilized powder, depending on the intended route of administration. The drug is then packaged in appropriate containers under sterile conditions for storage and distribution.

5.3 Therapeutic uses:

1. Multiple Myeloma: Plitidepsin has demonstrated activity against multiple myeloma, a cancer that affects plasma cells in the bone marrow. It works by inhibiting the growth of cancer cells and inducing apoptosis (cell death) in multiple myeloma cells. Plitidepsin has been investigated in clinical trials, both as a single agent and in combination with other drugs, showing promising results in terms of response rates and progression-free survival.
2. Lymphoma: Preclinical studies have suggested that plitidepsin may have activity against various types of lymphomas, including non-Hodgkin lymphoma. It has been shown to inhibit the growth of lymphoma cells and induce cell death. Clinical trials are ongoing to further evaluate its efficacy and safety in lymphoma patients.
3. Solid Tumors: Plitidepsin has also demonstrated activity against solid tumors, including ovarian, breast, and prostate cancers. It exerts its anticancer effects by interfering with various cellular processes involved in tumor growth and metastasis. Clinical trials are being conducted to evaluate its efficacy and safety in patients with solid tumors.
4. Hematological Malignancies: Apart from multiple myeloma and lymphoma, plitidepsin has shown potential activity against other hematological malignancies, such as acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL). It has been investigated in preclinical and early-phase clinical trials for these indications.

Acknowledgements

The authors acknowledging Nehru College of Pharmacy, Pampady, Thiruvilwamala, Thrissur, Kerala for providing all the support.

References

Tejswini Devidas Navgire (2021). *Study of marine drugs. International Journal of Creative Research Thoughts*,2021, 9(9), 729- 737.

S.Vignesh, A.Raja & Arthur James (2011). *Marine drugs: Implication and future studies*. International Journal of Pharmacology, 2011, 7(1), 22-30.

Modak Dwiti (2015). *Marine pharmacognosy: An overview. International Journal of Scientific Progress and Research*, 2015, 12(2), 55-59.

Sherif S Ebada, Ru Angelie Edrada, Wenhan Lin & Peter Proksch (2008). *Methods for isolation, purification and structural elucidation of bioactive secondary metabolites from marine invertebrates*. Nature Protocols, 2008, 3(12), 1820- 1831.

Joseph G McGivern (2007). *Ziconotide: A review of its pharmacology and use in the treatment of pain*. Neuropsychiatric Disease and Treatment, 2007, 3(1), 69- 85.

Jun Ho Yi, Seok Jin Kim & Won Seog Kim (2017). *Brentuximab vedotin: Clinical updates and practical guidance*. An International Journal Discovering All About The Blood, 2017, 52(4), 243-253.

Peter D Senter & Eric L Sievers (2012). *The discovery and development of brentuximab vedotin for use in relapsed Hodgkin Lymphoma and systemic anaplastic large cell lymphoma*. Nature Biotechnology, 2012, 30, 631- 637.

Jorge Lago, Laura P Rodriguez, Lucia Blanco, Juan Manuel Vieites & Ana G Cabado (2015). *Tetrodotoxin, an extremely potent marine neurotoxin: distribution, toxicity, origin and therapeutical uses*. Marine Drugs, 2015, 13(10), 6384- 6406.

Michail Papapanou, Eleni Papoutsi, Timoleon Giannakas & Paraskevi Katsaounou (2021). *Plitidepsin: Mechanisms and clinical profile of a promising antiviral agent against covid-19*. Journal of Personalized Medicine, 2021, 11(7), 668- 675.

P. Guisado- Vasco, M. M Carralon- Gonzalez, J. Aguareles- Gorines, E. M Marti- Ballesteros, M. D Sanchez – Manzano, et al.(2022). *Plitidepsin as a successful rescue treatment for prolonged viral SARS-CoV-2 replication in a patient with previous anti-CD20 monoclonal antibody-mediated B cell depletion and chronic lymphocytic leukemia*. Journal of Hematology & Oncology, 2022, 15(4)