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A REVIEW ON MARINE PRODUCT BRYOSTATIN 1: A PROTEIN KINASE C ISOZYME MODULATOR

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ABSTRACT

Natural products obtained from marine sources are endowed with promising pharmacological activities, thus representing invaluable leads in the drug discovery. The aim of this review is to highlight the work on natural marine product Bryostatin 1 with around 20 naturally available derivatives. This review compiles the comprehensive updated information of Bryostatin 1 including its biological source, geographical distribution, structure, characterization, synthesis and its role as isozyme Protein kinase C inhibitor. Also detail of role of Protein kinase C in Alzheimer and cancer pathology and relevance of Bryostatin 1. It is found to be enhancing memory and improving behavior in Alzheimer disease and it also enhances memory in normal person. The research for Alzheimer disease is in phase II clinical trial.

This work encourage the researchers for further work on the marine product. The comprehensive information from the review will be helpful for researchers to focus on the preferential research areas yet to be examined and after structural modification of Bryostatin can be exploited as lead molecules for other pharmacological activities.

Keywords: Bryostatin1; Marine product; Protein kinase C

INTRODUCTION

The earth covers 71% water and 29% land and the sea holds 96.5% water of earth which consist variety of plants and organisms. Indo-pacific ocean contains around 1000 species for each square meter in the certain regions, which is a vast biodiversity region. The organisms like sponge who lives in ocean water and feeded themselves by filtering the ocean water. As per the experts they protect themselves from hunters and microbes by their anti-microbial and anti-infective property. This property provides the link between marine drugs and human health. The drugs which are derived from marine source are used in different diseases such as Cancer, Alzheimer, depression, skin diseases etc. Cancer cells are rapidly growing and spread in whole human body, so the feature rapid killing of harmful bacteria provides reference for new anticancer agent. Bryostatin 1 drug has been one of the anticancer drugs. Bryostatin 1 is obtained from *Bugulaneritina bugula*. In 1968, first sample of *Bugulaneritina* screened for anticancer activity by National Cancer Institute (NCI) and their collaborators **[1, 2]**. In 1980, A scientist Cherry Herald with George Petite collected the 500 kilograms of *Bugulaneritina* species and isolated first milligrams amount of Bryostatin 1 drug **[3]**. The Bryostatin compound contains family of 20 macrolide lactone in which 19 are structurally contains bryophan ring. Bryostatin 1 is most studied member in Bryozoans family, which includes more than 40 clinical study trials. It shows beneficial effect in different diseases using Protein Kinase C (PKC) isozyme **[4]**. PKC plays role as transfer of signal to cell differentiation and cell proliferation that relatively effective against neoplastic transformation.

STRUCTURE

Bryostatin 1 insoluble in water and has molecular formula $C_{47}H_{68}O_{17}$. The first structure of Bryostatin 1 is noted in 1982 **[5]**. Bryostatin 1 is structurally suitable for PKC binding activity for their isoforms. The C-26 free hydroxyl group needs to form better interaction with isozyme of PKC. The C-1 carbonyl group in structure is important for higher affinity. The hydroxyl group C-19 interacts with lipid bilayer and C-3 hydroxyl group plays role in maintaining required conformation of molecule **(Figure 1)**.

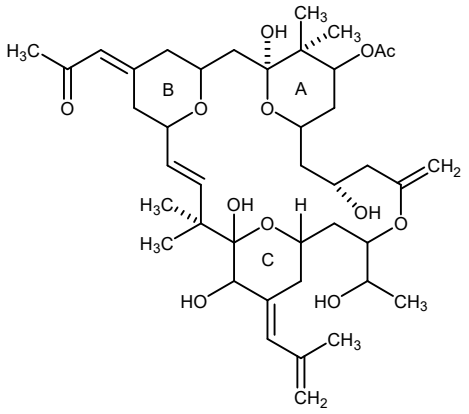

Figure 1: Structure of Bryostatin 1

The structure of Bryostatin 1 drug derived in three ring region-A type, B-type and C-type. In this types, region A can be modified or change in larger area without affecting binding activity, because of that the C-9 region can be change as to get required pharmacokinetic property, non pharmacophoric site can also change according to physicochemical property without affecting PKC isozyme binding property. B ring majorly responsible for activation of protein kinase isozyme and it shows greater structural and functional property **[6]**.

Absolute stereochemistry of Bryostatin 1 drug was determined by X-ray method by George Petite and his coworkers. They said that it shows three pyran ring and in chair form. The fourth position substituent of pyran ring seen as projected outward **[7]**. After initiation of structural elucidation other nineteen structures were observed **[3]**.

Structural determination of component from marine source using spectroscopy method is generally mass spectroscopy and nuclear magnetic resonance spectroscopy. It may also used chemical methods,and absolute stereochemistry.

ISOLATION

Isolation and synthesis of drugs should be carried out by using current good manufacturing practice (CGMP). This cGMP control manufacturing, synthesis, quality, strength, purity of drug, avoid the contamination and make product good for human health as per the guidelines.

In 1982, George Pettite used 500kg Bugulaneritina and isolated 120g of Bryostatin 1 and determined structure of drug **[2]**. In 1988, the large amount (14 tons) of Bugulaneritina was collected from California coast shallow water. Those collected samples stored in surrounding known temperature in isopropyl alcohol and extracted with methanol. Those mixed methanol and

isopropyl alcohol were concentrated and separate with the ethyl acetate. Ethyl acetate fraction was used as starting material in isolation process. Starting elute contains decreased mass and concentrates of Bryostatin. After increase in hexane component Bryostatin 1 separate through Bryostatin 2 **[8]**. For purification of drug they used HPLC with PDA detector. In result, off white colour powder of Bryostatin 1 drug is formed. The overall quantity of Bryostatin 1 drug was 18g only. This isolation phase completed in 10 months. The percentage yield for Bryostatin 1 drug was very less but enough for trials. Basic steps to prepare drug from natural marine source as shows in **(Figure 2)**.

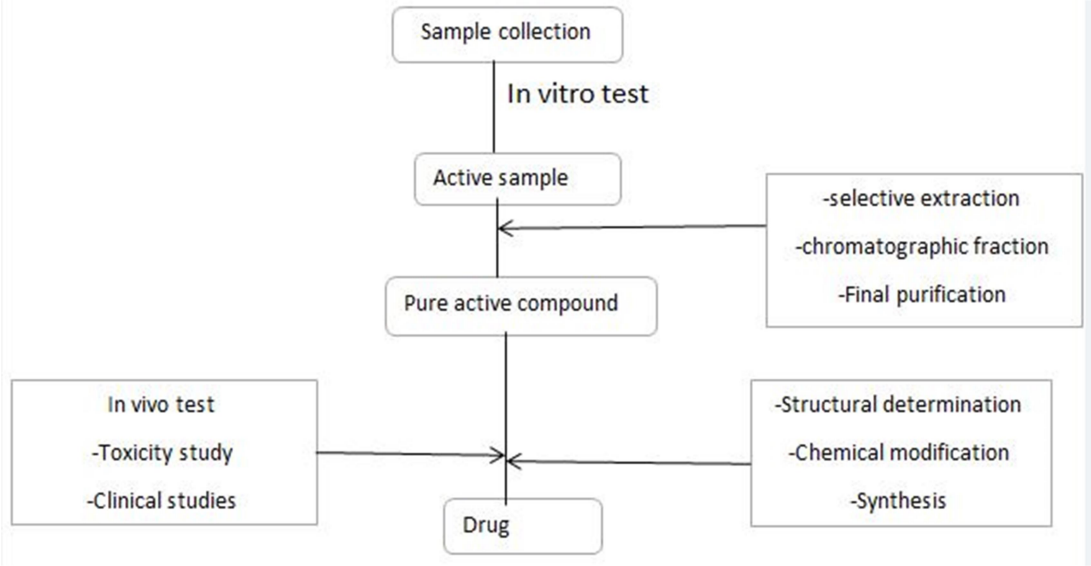

Figure 2: Isolation of Bryostatin 1

Steps for isolation of drug are different with their variety, availability and polarity. Extract contains active lead crude drug. This lead crude drug mixed with the suitable solvent. Methanol and acetone are most used as a solvent. The mixed drug with solvent distribute as their polarity which may be low, medium and high polarity. Drug containing low or medium polarity used standard normal or reversed phase column chromatography for separation and in final stage. HPLC is used to get pure active compound. Similarly, high polarity solvents like methanol and water were used for isolation of pure active compound **[9]**.

SYNTHESIS

Isolation of 18g of Bryostatin 1 drug from 14000 kg of marine source Bugulaneritina

shows the less availability of drug. But, that Bryostatin 1 drug shows strong activity against cancer and Alzheimer disease. Therefore, the scientists were trying to make Bryostatin 1 drug synthetically in laboratory. Scientist Gary E. Keck and coworkers successfully synthesized in 2011. They made total synthesis of Bryostatin 1 drug in 58 steps **[10]**. Further study of drug by Paul Wender and his collaborator got succeed by made Bryostatin 1 drug using 29 steps in 2017.

A ring (1) and B ring (2) is combine by yamaguchi esterification and form intermediate (3), this undergoes ozonolysis gives keto group (4) by involving methanol to improve yield. Octynoate in C-20 position react with triphenylphosphine and 2,4,6 trimethyl phenol gives dienoate (5), Fuji's phosphonate (6) introduced B ring enoate, silyl ether and ketal (7) treated with HF pyridine and formed Bryostatin 1 drug **[11]** **(Figure 3)**.

ALZHEIMER DISEASE

Alzheimer disease is memory related disease, in which brain cell loses their connectivity and cell die or degrade, which leads to loss of memory. Literature review reveals that PKC isozyme exhibit good effect in Alzheimer disease; Therefore, Bryostatin 1 drug has been focused to treat Alzheimer disease. Bryostatin 1 drug increase the level of PKC, which causes increase in understanding and improvement in behaviour. Amyloid plaques and neurofibrillary tangles and disturb the microtubules joints that affect nerve cell which leads to cell neutralizing or death of cell, which result in loss of memory. Due to this quality of amyloid plaques and neurofibrillary tangles they are called as biomarkers of Alzheimer disease **[12]**. PKC isozyme helps for synaptic growth which is helpful for learning and memory. Reverse synaptic loss prevented by using Bryostatin 1 drug for transmission of neuronal signal Ca^{2+} is important factor so Bryostatin 1 starts up the PKC isozyme in neuron portion with calcium. This help to stimulate neuronal growth associated protein 43 (GAP-43). It increases the level of GAP-43 and help to enhance memory **[13]**. Increasing memory with reducing disturbance in amyloid plaques and neurofibrillary tangle in combination shows potential against Alzheimer disease.

Bryostatin 1 drug for Alzheimer disease reached upto phase-Ⅱ clinical trials for more than 40 times. Currently used Bryostatin 1 drug study showed that one gram of Bryostatin 1 can treat two thousand patients who suffering from Alzheimer disease **(Figure 4)**.

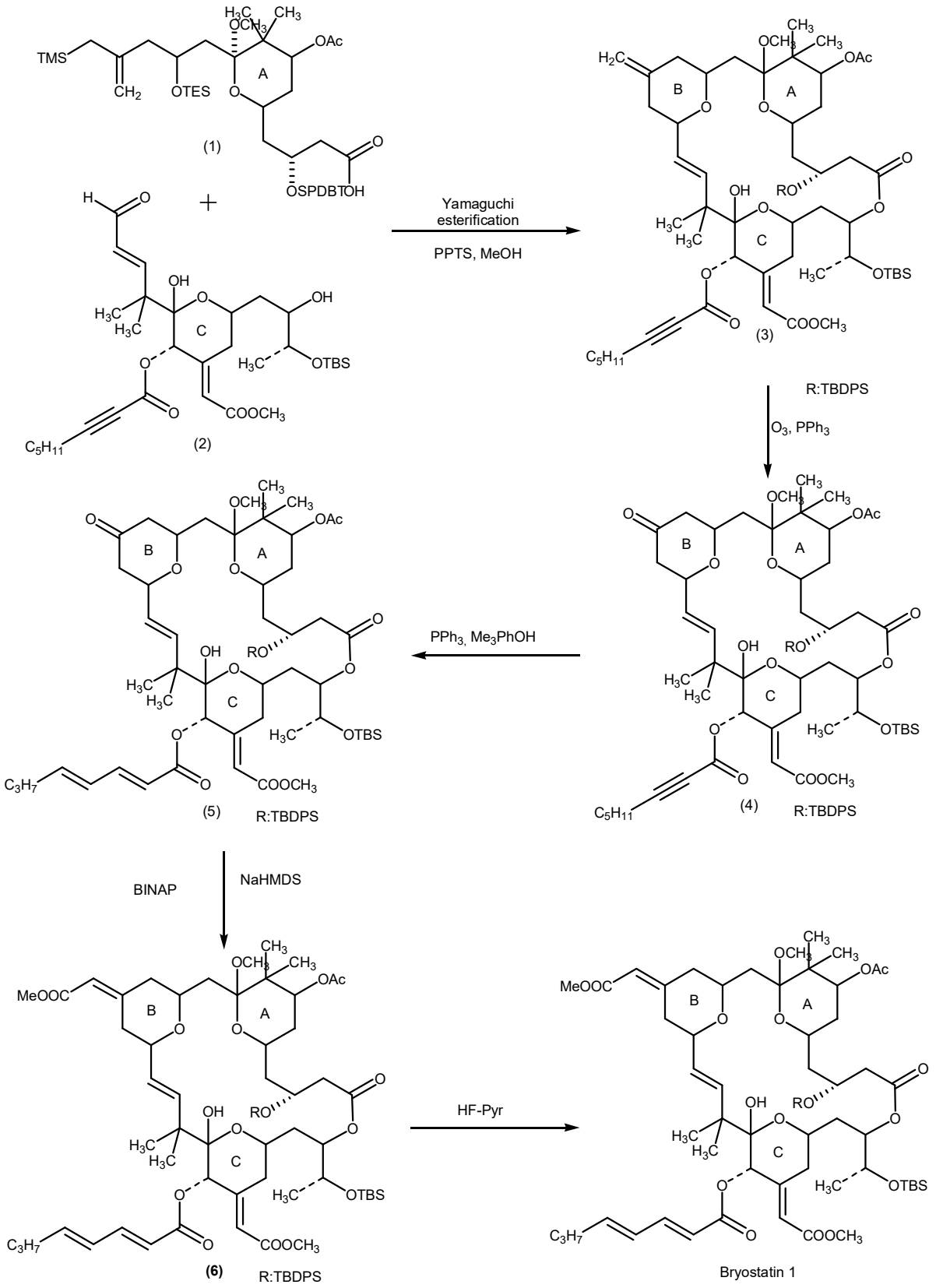

Figure 3: Synthesis of Bryostatin 1

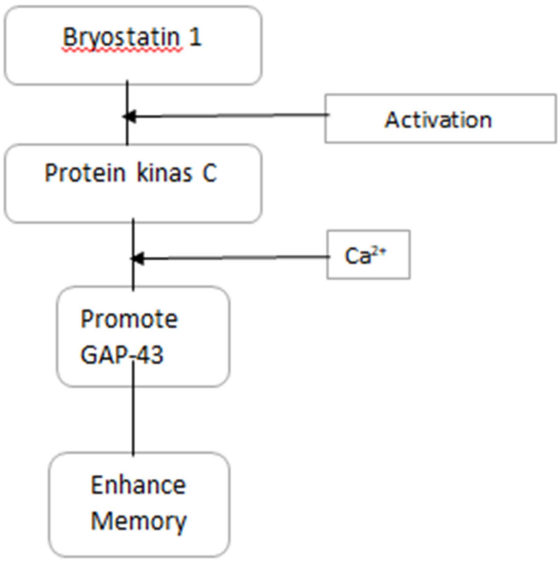

Figure 4: Role of Bryostatin 1 in memory enhancement

CANCER

PKC isozyme is a strongest part for Bryostatin 1 drug to show effect against cancer disease. Activation of PKC isozyme and transfer to nuclear membrane with Bryostatin 1 drug when contact duration is small. PKC isozyme reduces their activity when in contact with Bryostatin 1 for long time because the ability of PKC enzyme decreases **[14]**. Bryostatin 1 drug studied for different types of cancer. In phase-1 clinical trials Bryostatin 1 drug gives antitumor effect. In phase-Ⅱ trials Bryostatin 1 used lonely, in result it gives melanoma type cancer effect, toxicity and muscle paining. Due to this effect there is rise in the plasma concentration of TNF-alpha and IL6, for inhibition of PKC activity **[15]**. Use of Bryostatin 1 with pacitaxel leads decreased growth of tumour. Bryostatin 1 shows toxic effect when it used alone, so they examined Bryostatin 1 with other cytotoxic agent to know efficacy against different types of cancer disease. One of them is Paclitaxel drug with combination of Bryostatin 1 drug shows great response against esophageal and gastro esophageal type of cancer **[16, 17]**. Bryostatin 1 in combination with vincristine shows efficacy in patient but also show abnormal beta lymphocytes (beta cell non-Hodgkin's lymphoma) **[18, 19]**.

Some related studies were published by research group of Ramzi Mohammad. In those studies they concentrate on effect of

Bryostatin 1 as anticancer agent. They used the combination of Bryostatin 1 drug with other marine drug (Dolastatin 10). They found that combination is only partially effective. They used structurally modified Soblidotinin combination with Bryostatin 1 and found that combination was totally effective against tumor **[14, 20]**.

CONCLUSION

This review compiles the comprehensive updated information of Bryostatin 1 including its biological source, geographical distribution, structure, characterization, synthesis and its role in related to affinity with isozyme PKC and its effectiveness in treatment of cancer and alzheimer disease. In alzheimer disease it is enhancing memory and behaviour and it also enhances memory in normal person.

The current review reveals that 1 mg of Bryostatin 1 is used for clinical trials shows that it is very potent molecule and reached upto phase-II clinical trials. If it is isolated from marine source its yield is very less (0.00014%) therefore successful efforts are made to synthesize it in laboratory and can be derivatized to get successful lead and may be one of the potent drug in future.

The comprehensive information from the review will be helpful for researchers to focus on the preferential research areas yet to be examined and after structural modifications it can be exploited as lead molecules for other pharmacological activities related to CNS diseases.

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CONFLICT OF INTERESTS

The authors report no declarations of conflict of interest regarding publication of this article.

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