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MOLECULAR MECHANISMS OF BIOSYNTHESIS & PHARMACEUTICAL ACTIVITIES OF MARINE NATURAL PRODUCTS: AN OVERVIEW AND FUTURE OUTLOOK FOR DRUG DISCOVERY

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ABSTRACT

There are hundreds and thousands of compounds of marine natural product that are used for medicinal use from the present decades. These compounds are used for therapy of different infectious diseases like HIV, cancer, tumor, and analgesic. These compounds are synthesized and modified and make them useable for the treatment of different diseases and having numerous characteristics in medical field extracted from marine organism. These compounds of marine organisms are further modified with high specificity for the discovery of new drugs in present and near future.

Keywords: Marine Alkaloid, Medicinal Importance, Drug Discovery, Anti-Carcinogenic, Plants Microbes

1. INTRODUCTION

In chemistry, marine natural products are used for the synthesis and extraction of new compounds that can be used as therapy agents. The research was initiated when marine bioactive compounds were identified. Caribbean sponges, tectitethya crypta, a marine sponge characterized and identified with their biological significance, have taken on an increasing importance as marine natural products. To synthesize different analogs of different nucleosides, the researcher attached

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nucleoside bases to sugar moieties and substituted pentose sugar through acyclic units. Antiviral, antitumor, and analgesic drugs can be synthesized using these nucleosides. As DNA chains elongate, these nucleosides inhibit the chain and polymerize with the elongation of DNA chains [1-2]. Besides sponges, bacteria and fungi are also sources of natural products with potential biological activity [3]. This marine natural product was the first isolated and characterized as possessing industrial properties. It is derived from polychaeta worms belonging to the species *Lumbrinereis* nereistoxin is used to control insect plagues in orange plantations, sugarcane fields, and rice fields [4-5]. As an example, the pesticide Cartap is low toxicity to humans but high in efficacy when ingested purposefully. In addition to acting as a cell cycle regulator, okadaic acid can act as an effective antitumor drug. [6a].

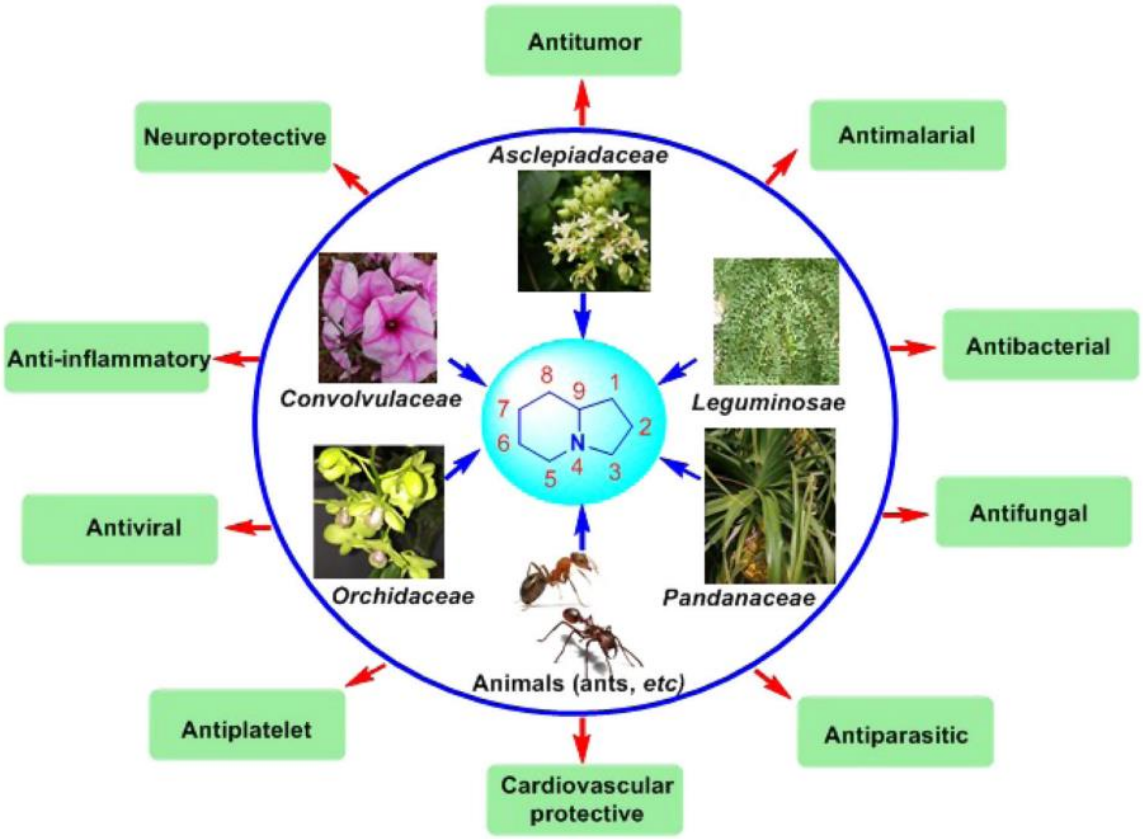

Fig 1. Biological significance of indolizidine alkaloids

The last three decades have witnessed significant biological activity demonstrated by marine compounds against in vitro cytotoxicity. Furthermore, invertebrates of the family *Cnidaria* and *Porifera* have also been found to contain compounds that show good activity against microbes since 1985 [7]. Over the past eight years, marine organisms have produced thousands of new compounds with significant biological properties [8]. This article will discuss marine natural products that are extracted from marine organisms as well as their mode of action and mechanism, along with their medicinal and biological importance.

The underlying architecture, the components that are readily accessible, and the overall picture of the biological activity of indolizidine alkaloids. The essential structure of indolizidine alkaloids is comprised of a ring with 5 members that is connected with a ring that has 6 members and a nitrogen atom in common. Together, these two rings make up the indolizidine alkaloid. The pharmacological effects of indolizidine alkaloids include, but are not limited to, those that are antibacterial, antifungal, anti-inflammatory, antimalarial, antiparasitic, antiplatelet, antitumor, antiviral, cardiovascular protective, insecticidal, neuroprotective, and anti-Alzheimer's disease [6b], etc., but this list is not exhaustive are shown in (figure 1)

2.1 . BIOSYNTHESIS OF OROIDIN MARINE ALKALOID

Lysine (**2**) is detected to be the basic precursor of 2-aminoimidazole moiety of oroidin (**11**) while arginine and ornithine (**8**) are responsible for the synthesis of proline (**9**) (although there is ten percent less conversion of these into oroidin because of the urea cycle we can see in mechanism) [9]. Lysine, homoarginine, arginine and ornithine (**8**) are the four amino acids which are the precursors of 2-aminoimidazole moiety. Lysine is converted into homoarginine by a series of steps (including urea cycle). Later then, the homoarginie is oxidized into γ-hydroxyhomoarginie. On the other hand, the pyrrole has been converted into pyrrole-2-carboxylic acid by several micro-organisms as enzymes. Then the resulting subsequent steps of oxidation and condensation lead to the final product of oroidin (**11**). This was the best suggested mechanism and was presented by Lindel [10-11].

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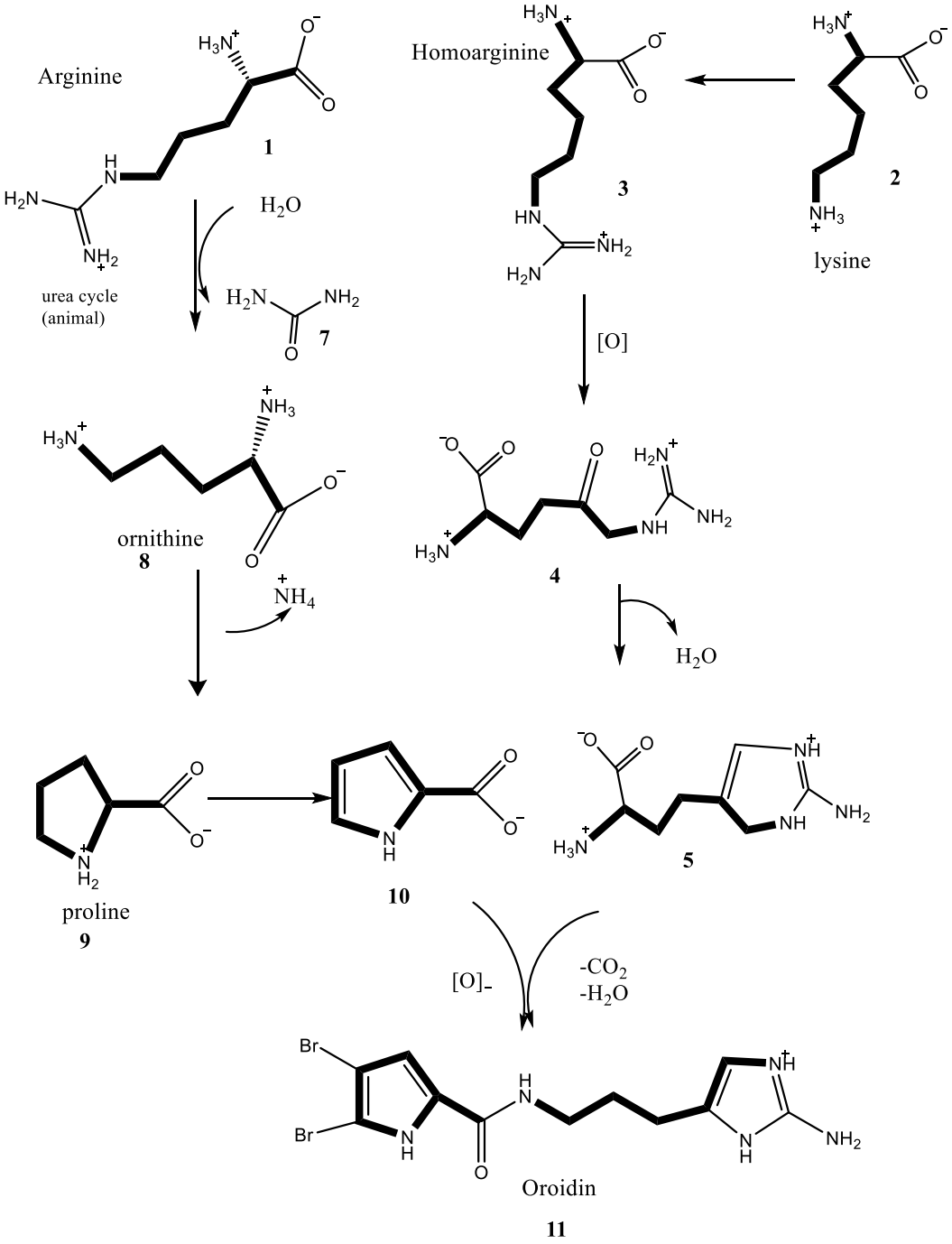

Scheme 1. Biosynthesis of oroidin alkaloid.

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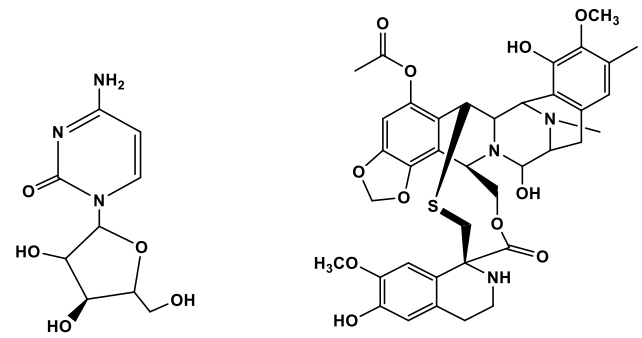
2.2. ANTITUMOR MARINE ALKALOIDS

Marine natural product base four drugs have jumped into the market to treat cancer and nine drugs are under clinical. The study of these drugs indicated that in some cases their mode of action is unique. Among their different mechanism of action, these drugs target apoptosis and the transcription factor NF-κB [12]. In order to synthesize analogs such as Cytarabine and Ara-C (**12**), the nucleosides were used as model from the sponge *Tectitethya crypta*. Ara-C showed its potency against leukemia and lymphoma and was approved for used in 1972. Marine based antitumor drug is ecteinascidin-743 (**13**) or trabectedin or ET-743. ET-743 has broad spectrum antitumor agent and was discovered by researcher of Illinois University (USA) [13]. ET-743 (**13**) structure contains tetrahydroisoquinoline and was produced by the tunicate *ecteinascidia turbinate*. Et-743 enters the minor groove of DNA molecules causes hindrance in the DNA transcription, cell division and repair mechanism. Forty years were spent from isolation to consent by FDA and EMEA [14].



Cytarabine or Ara-C
12

Trabectedin (ET-743)
13

Figure 1. Antitumor analogues of marine alkaloid analogues.

Another Marine based potent antimitotic drug is dolastatin (**14**). Two sources of dolastatin (**14**) had been reported and first source is *dolabella auricularia* and other is the cyanobacteria [15]. Dolastatin-15 (**3**) analogs were developed. Tasidotin hydrochloride (ILX-651) (**16**) developed by

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BASF pharma and reached phase I of clinical trials to treat new dangerous tumors of pancreas, lung, colorectal, and kidneys [16]. For melanoma disease, the analog cematodin (LU-103793) (**15**) was prepared and reached phase-II of medical trials. It was prepared by a Germany company ABBOTT GmbH & Co. KG [17].

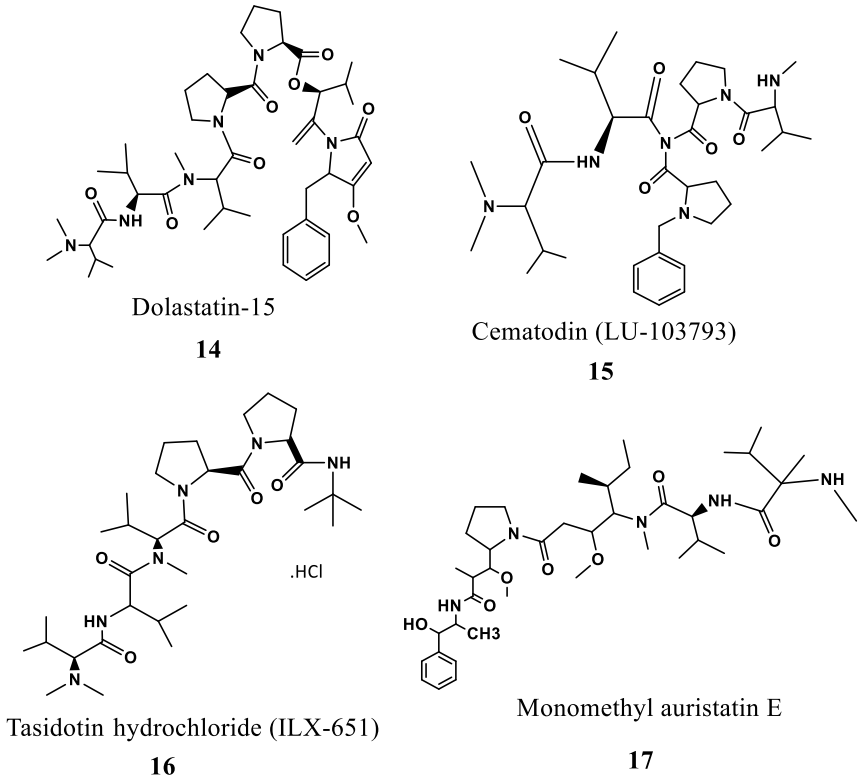

Figure 2. Antitumor alkaloids analogues.

Dolastatin-10 was reached phase II of medical trials but then it was taking back [18]. After some years, the analog of dolastatin-10 was prepared, and it was named as monomethyl auristatin E (**17**) and it was joined with antibody. This analog expressed efficacy against carcinoma.

2.3. ANTIVIRAL MARINE ALKALOIDS

Marine natural products based antiviral drugs are also important. With a semi-synthetic modification in the structure of nucleoside spongouridine (**18**), the analogs prepared were vidarabine/Ara-A/Vira-A (**19**), aciclovir (**20**), and zidovudine or azidothymidine or AZT (**21**) [19].

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After the synthesis of vidarabine (**19**) [20], it was also prepared by the fermentation of *Streptomyces antibioticus* and it was famous as vira-A in market since 1976. Vidarabine plays an important role to inhibition DNA polymerases of different viruses which were varicella-zoster, vaccinia and herpes [21]. It is also recommended to cure herpes virus related conjunctivitis.

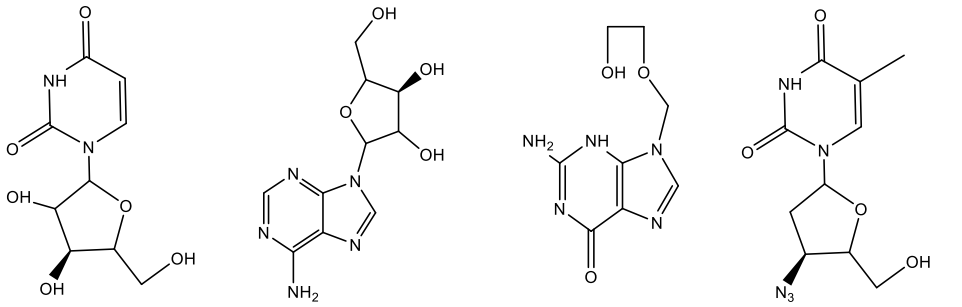

Figure 3. Antiviral analogues of marine alkaloid.

Other antiviral drug aciclovir (zovirax) is the analog of guanosine and used for the treatment of diseases caused by different viruses which were varicella viruses, zoster and herpes simplex [22]. If a person got infected by herpes simplex infections, first drug that recommended is aciclovir. Some prodrugs are also present in the markete i.e., valaciclovir [23]. Similarly, P. Horwitz was the first who synthesized AZT in 1964 as potential anticancer agent. After twenty years, this drug appeared to be as antiretroviral drug and inhibits the HIV reverse transcriptase (RT-HIV) [24]. The drug AZT entered the market in 1987 with trade name Retrovir. It was the first recommended drug for HIV patients. Due to its safety and efficacy, many nucleoside analogues were constructed i.e., THIV inhibitors such as abacavir (ABC), lamivudine (3TC) etc. In antiretroviral therapy, these elements still play their part.

2.4. ANALGESIC MARINE ALKALOIDS

Marine natural products-based drugs are very important to treat morphine-resistant patients. One marine natural product-based drug is ziconotide (**21**) that is available in market and other is tetrodotoxin (**22**) that is under medical trials (shown below).

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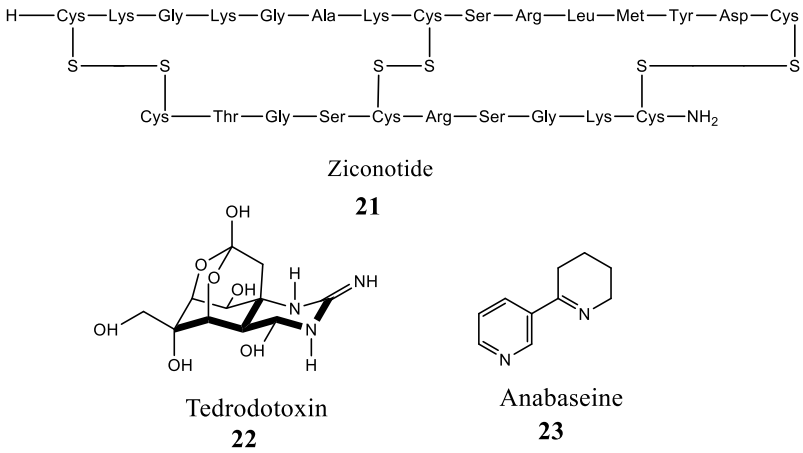

Figure 4. Anticancer analogues of marine alkaloid.

Mussels such as Conus magnus produce a peptide called ziconotide, also known as ω-conotoxin MVIIA. It was synthesized by Neurex Corporation EUA and cognetix Inc. EUA. It blocks the N-type Channels of Calcium that leads to the reduction of chronic and neuropathic pain [25-26]. The spasticity caused by spinal cord injury is decreased by the effect of ziconotide to decrease the upper and lower limbs reflexes [27]. Ziconotide market name is Prialt® and it was launched by Elan Pharmaceuticals in 2004 to treat chronic pain of morphine resistant-patients due to its important antinociceptive action. It is necessary to administer the Prialt by intrathecal route. So, it's used is confined to hospitals [28-29].

The sources of tetrodotoxin (TTX) are fish, algae and bacteria. It is used for cancer patient to sooth pain. It blocks the sodium channels that depend on voltage. WEX Pharmaceuticals Inc. from Canada is doing medical trials to its two formulations that are under phase II and III. Phase II form is for peripheral & cancer-related pains while Phase III is for cancer patient to soothe neuropathic pain by intramuscular & subcutaneous routes. Currently a review on tetrodotoxin toxicity & its chemistry was published recently [30].

2.5. BIOACTIVE ANTIBIOTICS MARINE ALKALOIDS

Effect Anticancer antibiotics are anthracycline, actinomycin, and aureolic acid families [31-32]. Peptolides, dactinomycin (**25**) are clinically valuable members of these families. They target many

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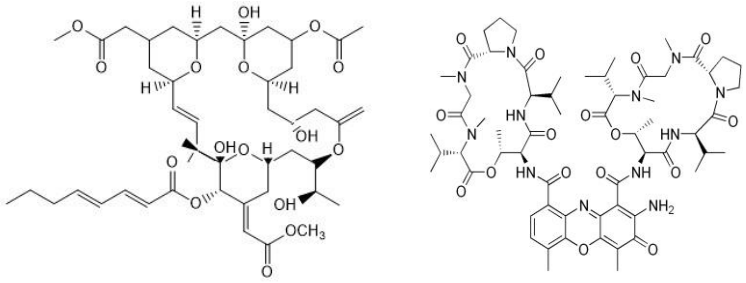
gliomata metabolic enzymes of the lipogenesis, glycolysis and glutaminolysis and might show a different anti-glioma mechanism of actinomycin-D [33]. Anthracyclines are among the most widely used antitumor antibiotics and inhibit topoisomerase-II [34-35]. When benzoquinone ansamycin is naturally fermented geldanamycin is obtained. Geldanamycin functions as inhibitor of heat shock protein HSP90 [36] and express cytotoxic effect against HeLa cells [37]. A comparison was made between a combination of trabectedin and pegylated liposomal doxorubicin and pegylated liposomal doxorubicin alone. This comparison was made to defeat the ovarian cancer in vivo. The three fused tetrahydroisoquinoline rings of trabectedin is the main cause of its efficacy. When it links covalently to the minor groove of DNA and come in contact with transcription factors (e.g., SP-1) straightaway, it blocks the transcription interacting effect and significant DNA [38]. Bryostatin (**24**) is another anticancer agent that modifies paclitaxel inhibitor of protein kinase C (PKC) [39].



Bryostatin-1
24

Dactinomycin
25

Figure 5. Bio-active antibiotic analogues of marine alkaloid.

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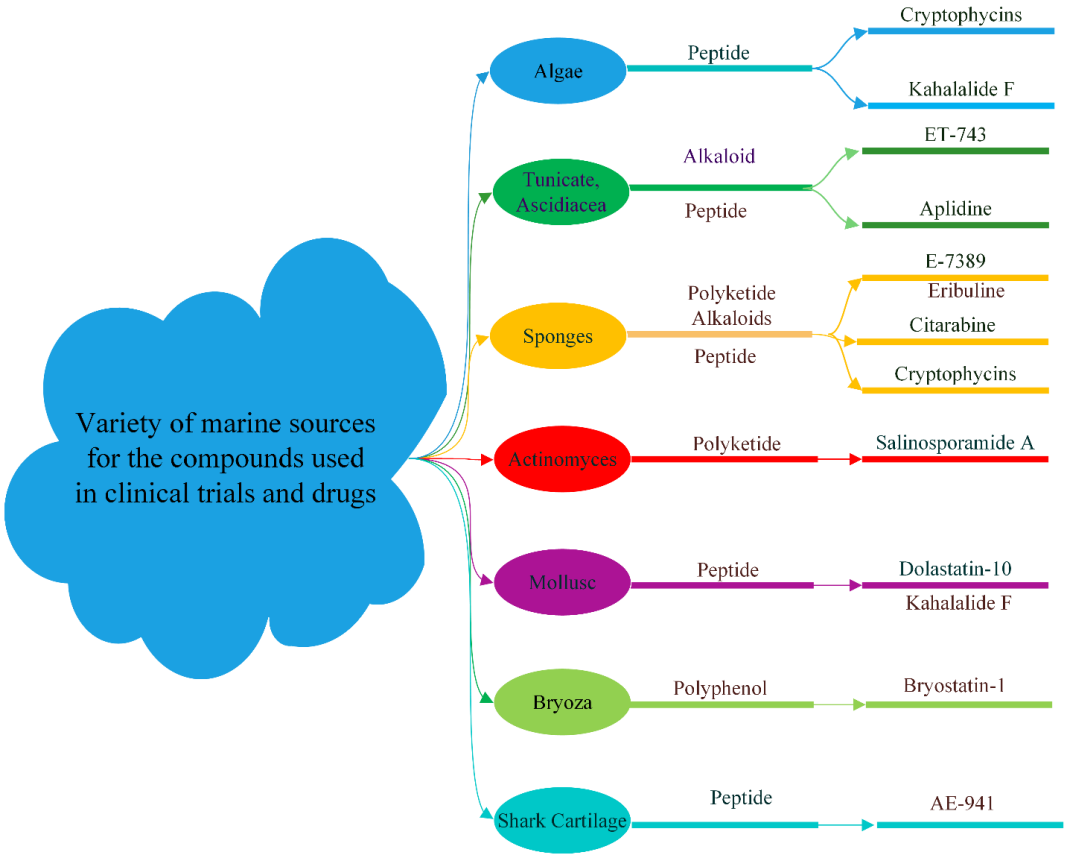

Figure 6. Clinical trials of marine alkaloids.

CONCLUSION

The above review article discus the various biological and medicinal application of various marine natural products briefly. Natural products derived from marine ecosystems play a crucial role in drug discovery, and multiple mechanisms are used to synthesize and modify drugs. The discovery of numerous drugs is mainly focus on infectious disease like analgesic, anti-tumor and especially anticancer therapy. The mode of action and their mechanisms of various marine alkaloids were first toxic in nature and could make possible through various modifications steps makes them for pharmaceutical applications. There have been thousands of marine alkaloid products isolated in recent decades because of the expanding application of marine alkaloids. A modification of these marine alkaloids was made after the isolation, according to the specific drug design and drug development. Marine ecosystems are populated with both macro- and micro-organisms. The

survival of these organisms is completely dependent on bio-synthetical activities. In order to combat microbes, these activities will be helpful. These isolated marine alkaloids were found to work significantly against infectious diseases during clinical trials of these marine alkaloids. As the number of compounds grows, it will become necessary to divide these alkaloids based on their taxa and phyla. In the following phases, we will study pharmacokinetics in order to learn more about the medical and pharmaceutical importance of marine alkaloids. It is a challenging task for drug development and drug design to elucidate the medicinal importance of marine alkaloids, but cooperation with organic and bioinformatics researchers can overcome this challenge. It is easy to explore marine alkaloids based on their therapeutic importance. Therefore, marine alkaloids are expected to have a bright future in both the medicinal and pharmaceutical industries for designing and developing new drugs.

Conflicts of interest the author has no conflict of interest and the idea of article is to create awareness among the general populace.

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