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Chapter

Antimicrobial Peptides Derived from Ascidians and Associated Cyanobacteria

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Abstract

Ascidians belonging to Phylum Chordata are the most largest and diverse of the Sub-phylum Tunicata (Urochordata). Marine ascidians are one of the richest sources of bioactive peptides. These bioactive peptides from marine ascidians are confined to various types of structures such as cyclic peptides, acyclic peptides (depsipeptides), linear helical peptides with abundance of one amino acid (proline, trytophane, histidine), peptides forming hairpin like beta sheets or α-helical/β-sheet mixed structures stabilized by intra molecular disulfide bonding. Cyanobactins are fabricated through the proteolytic cleavage and cyclization of precursor peptides coupled with further posttranslational modifications such as hydroxylation, glycosylation, heterocyclization, oxidation, or prenylation of amino acids. Ascidians are known to be a rich source of bioactive alkaloids. β-carbolines form a large group of tryptophan derived antibiotics. Pyridoacridines from ascidians are tetra- or penta- cyclic aromatic alkaloids with broad range of bioactivities. Didemnidines derived from ascidian symbiotic microbes are inhibitors of phospholipase A2 and induce cell apoptosis. Meridianins are indulged in inhibiting various protein kinases such as, cyclindependent kinases, glycogen synthase kinase-3, cyclic nucleotide dependent kinases, casein kinase, and also implicate their activity of interfering with topoisomerase, altering the mitochondrial membrane potential and binding to the DNA minor groove to inhibit transcriptional activation. Most of these bioactive compounds from ascidians are already in different phases of the clinical and pre-clinical trials. They can be used for their nutraceutical values because of their antineoplastic, antihypertensive, antioxidant, antimicrobial, cytotoxic, antibacterial, antifungal, insecticidal, anti-HIV and anti-parasitic, anti-malarial, anti-trypanosomal, anti-cancer etc. This chapter mostly deals with antibacterial compounds from ascidian and their associate symbiotic cyanobacteria.

Keywords: Ascidians, Chordata, depsipeptides, β-carbolines, pyridoacridines

1. Introduction

Ascidians commonly known as tunicates or sea squirts are soft bodied and sessile animals belonging to subphylum urochordates. Sac like sea squirt ascidians produce many toxic nitrogen bearing secondary metabolites that are implicated in their chemical defense [1]. Ascidians belonging to family *Didemnidae, Prochloron* species symbiotic bacteria produce a variety of toxic and cyclic peptides known

as cyanobactins [2]. Ascidians of this family have yielded structurally unique and pharmacological compounds such as didemnenones, enterocins, paterallazoles, varacins and virenamides [3]. Didemnin, isolated at first from the Caribbean tunicate *Tridemnin solidum*. Didemnin B capable of antiproliferative activity against human cancer cell lines. Didemnin B inhibits the synthesis of RNA, DNA and proteins [4]. It is found that Didemnin B being the first natural marine derived peptide to be evaluated in clinical trials, because of its dose-dependent and tolerable toxicity profiles. Toxicity profile of Didemnin B with dose dependent nausea and vomiting are the most commonly mentioned side effects [4]. However at the higher doses, Didemnin B causes severe cardiotoxicity.

Aplidine is a cyclodepsipeptide has sufficient activity against a variety of human cancer cell lines such as breast, melanoma and lung cancers [5]. Aplidine has several functional activities such as Inhibition of protein synthesis, cell cycle arrest, induction of apoptosis on cancer cells and inhibition of vascular endothelial growth factor gene. Its actions on causing cytotoxicity, involves the inhibition of ornithine decarboxylase, an enzyme that is responsible for the tumor formation and tumor growth [6]. Its approval on Phase-I clinical trial, induces on its minor toxicity tolerance limit with most of its side effects corresponding to asthenia, nausea, vomiting and transient transaminitis etc. [7].

Mollamides being a cyclodepsipeptide has suitable cytotoxic activity against a wide range of cancer cell lines such as human lung carcinoma and human colon carcinoma [8].

Trunkamide A, a cyclodepsipeptide with a thiazoline ring similar to mollamide, show antitumor activity under preclinical trials [9]. This peptide contains the thiazoline-based proline on doubly prenylated cyclopeptides. Heterocyclic amino acids such as the tryptophan and histidine also forms the part of proline rich cyclic peptides structures such as wainunuamide, phakellistatin 15,17 and stylissatin B.

However, recently pharmaceutical industries are gaining more insights on antimicrobial peptides due to their increased efficacy, high specificity, low toxicity, decreased drug interaction and direct attacking properties.

2. Alkaloids

Alkaloids are providing the majority of ascidian originating bioactive compounds. They represent a highly diverse group of compounds containing cyclic structures having a basic nitrogen atom incorporated within it. Ascidians on the other hand are produces of large quantity of alkaloids and modified peptides which exhibit a wide range of biological properties such as, Cytotoxicity, antibiotic, immunosuppressive activities, inhibition of topoisomerases (TOPO), cyclin kinase, display antimicrobial and anticancer activities by inhibiting kinase activity, including protein kinase B (PKB), Cyclin dependent kinases (CDKs), altering mitochondrial membrane potential and binding to the DNA minor groove to inhibit transcriptional activation [10].

Investigations on the biosynthesis of secondary metabolites provide evidence on the *de-novo* biosynthesis by ascidians [11]. Ascidians are a source of nitrogen bearing secondary metabolites with a varied range of biological activities. Many biological active compounds have been isolated from ascidians, it is still unclear whether this animal or associated microbial symbionts such as bacterial or fungi are true sources for the synthesis of biosynthetic metabolites.

A specific biosynthetic source of the alkaloids such as, granulatimide and isogranulatimides by specifically localizing these compounds lying inside ascidians.

Granulatimide stored in *Didemnum granulatum* tunic bladder cells were analyzed by confocal fluorescence microscopy at the granulatimide emission range, indicated the presence of fluorescent cells as highly vacuolated cells found to be dispersed in ascidian tunic [12]. Thus, this is the most exposed ascidian tissue, it pertains to show that this alkaloids may have a protective role.

2.1 Didemnidines

Didemnidines A and B are two indole spermidine alkaloids isolated from ascidian Didemnum species. Didemnidines A and B are both active as inhibitors of phospholipase A2, farnesyltransferase enzyme without cytotoxicity. It has moderate cytotoxicity towards malarial parasite, L6 cells and inhibition parasite proliferation. Antiparasitic activity of didemnidine B provides the opportunity to explore the didemnidines as antimalarial and antitrypanosomal agents [13].

2.2 Meridianins

Meridianins are brominated 3-(2-aminopyrimidine)-indoles isolated from the ascidian *Aplidium meridianum* [14]. As these meridianins are structurally similar to variolins, meridianins are identified as a promising kinase inhibitory scaffolds, which inhibits various protein kinases such as, Cyclin dependent kinases, glycogen synthase kinase 3, cyclin nucleotide dependent kinases and casein kinase [15].

2.3 Herdmanines

Herdmanines represent a series of nucleoside derivatives isolated from the ascidian *Herdmania monus*. Herdmanines A to D inhibit the production and the expression of messanger RNA, Pro-inflammatory cytokines, while herdmanines C and D are found to have moderate suppressive effects on the pro-inflammatory cytokines and lipopolysaccharides (LPS) induced nitricoxide [16].

2.4 Ecteinascidins

This peptide belonging to tetrahydroisoquinoline alkaloid family exhibits potent antitumor activity. It binds with the major groove of DNA and leads to the sequence specific alterations in transcription, triggers DNA cleavage, causing double stranded break, interruption of the cell cycle, apoptosis of cancer cell and down regulation of some transcriptional [17] factors.

2.5 Eusynstyelamides

Eusynstyelaides, alkaloids isolated from ascidian *Eusynstye latatericus*. It has specific cytotoxic activity against neuronal nitric oxide synthase (nNOS), anticancer and antibacterial activities. Eusynstyelaides B, a secondary metabolite from a bryozoan species, suggested that these components could be synthesized by symbiotic microbes. Eusynstyelaides B exhibits anti-proliferative activity and causes a strong cell cycle block and also induces cell apoptosis [18]. Eusynstyelamides A–C show specific cytotoxicity against neuronal nitric oxide synthase (nNOS) and show anticancer and antibacterial activity [19]. Eusynstyelamides A and B display, inhibitory activities against *Staphylococcus aureus*, plant regulatory enzymes pyruvate phosphate dikinase (PPDK) [20].

2.6 Sesbanimide

Sesbanimide A, peptide isolated from Agrobacterium. Sesbanimide C showed activity against the growth of mouse leukemia cells and inhibited the proliferation of mouth epidermal carcinoma (kb) cell [21]. It was evaluated against various human cancer cell lines.

2.7 Mollamide

A cyclodepsipeptide isolated from the ascidian *Didemnum molle*, shows specific cytotoxic activity towards a range of cell lines with IC 50 values of 1ug/ml towards P388murine leukemia cell lines and 2.5ug/ml resistance towards A549 human lung carcinoma and HT29 human colon carcinoma [22]. Neuromuscular toxicity with the elevation of creatine phosphatase levels has been dose limited, but seemed to be readily irreversible with oral carnitine. Aplidine has shown antitumor activity in phase-I clinical trials and in phase-II clinical trials in solid tumors.

3. Antimicrobial peptides from ascidians

Peptides are one of the major structural classes isolated from ascidians, including linear peptides, depsipeptides, and cyclic peptides, with residue numbers spanning from two to forty eight. Most of the active peptides from ascidians have complex cyclic of linear structures rarely found in terrestrial animals. These peptides are found to affect cell behavior with different mechanisms such as apoptosis, affecting the tubulin- microtubule environment and [23] inhibiting angiogenesis.

3.1 Vitilevuamide

A bicyclic peptide isolated from ascidian *Didemnum cuculiferum* and *Polysyncranton lithostrotum*. It was found that Vitilevuamide show activity against mouse lymphocytic leukemia. Its mechanism of cytotoxicity is due to its inhibition of tubulin polymerization without competitive inhibition of the vinblastine binding site, affects GTP binding to tubulin and also cell cycle arrest in the G2/M phase (**Figure 1**).

3.2 Diazonamides

A group of macrocytic peptides isolated from the ascidians *Diazona angulate*. Amoung various diazolzmides, Diazolamide A was evaluated for its antitumor activities [24]. It is a tubulin binding agent which blocks the cell cycle in G2/M period. Diazonamides A is a potentially chemotherapeutic agent without significant toxicity on animal models [25].

3.3 Chondromodulin-1 (ChM-1)

Chondromodulin, a 25kD a glycoprotein isolated from fetal bovine cartilage. Recently, Chondromodulin isolated from the invertebrate ascidian *Ciona savignyl*. It promotes the proliferation of mouse osteoblastic cell and also protects the H2O2 oxidation injury. Chondromodulin also modifies the cell behavior through regulating the cell cycle and cell adhesion [26]. It was found that Chondromodulin acts as a potential antioxidant and antitumor agent [27].

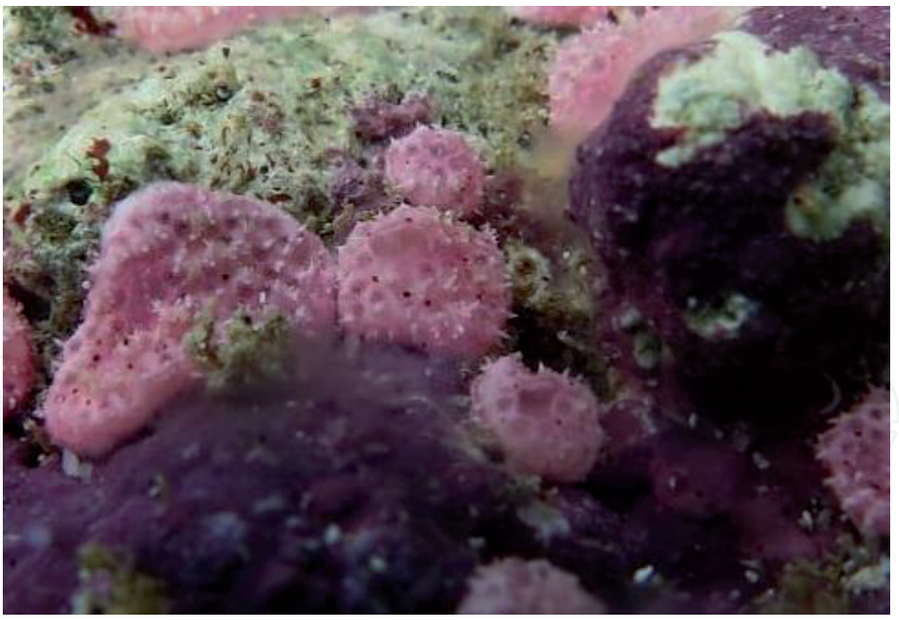

Figure 1.
Image showing Didemnum cuculiferum.

4. Polypeptide from ascidian associated microbes

4.1 Patellamides

Patellamides are cyclic peptides isolated from the cyanobacterium *Lissoclinum patella*. Patellamides A, C, D exhibits cytotoxic effects. Patellamides A and C inhibit the growth of murine leukemia cells, while patellamide D acts as a resistance modifying agent in the multidrug resistant human leukemia cell lines [28].

4.2 Polyketides

Polyketides are the other important compounds in the screening of secondary metabolites. Polyketides are complex molecules built from simple carboxylic acids and synthesized by polyketide synthetase [29]. Polyketides has been discovered as important lead compounds with various activities, such as blocking protein tyrosine phosphatase and inhibiting ATP synthetase complex [30]. Highly cytotoxic patellazole A, thought to have a defensive role, is a polyketide peptide hybrid made by the alpha-proteobacterium Ca. *Endolissoclinum faulkneri*. This bacteria was found only in a subgroup of *Lissoclinum patella*, and its genome is extensively reduced, that the bacteria is only found in a subgroup of *Lissoclinum patella*, and its genome is reduced, such that it cannot live independently in a host. These peptides are known to maintain all the synthesized genes, providing evidence for an essential defensive role of these metabolites in this symbiotic relationship [31].

4.3 Mandelalides

Mandelalides A-D are macrocyclic polyketides isolated from a new species *Lissoclinum mandelai* in south Africa. Mandelalides are glycosylated polyketides isolated from ascidian *Lissoclinum* (**Figure 2**). Mandelalides A and B show potent cytotoxicity towards, NCI-H460 cells and mouse Neuro-2a neuroblastoma cells. Mandelalides B display potent antifungicidal activity against *Candida albicans* [32]. Isomandelalide A exhibited unexpectedly high level of activity being more potent than mandelalide B. Glycosylated mandelalides A and B are cytotoxic to

Figure 2.
Image showing cyanobacterium Lissoclinum patella.

neuroblastoma cells at low nanomolecular concentrations. New mandelalides G-L isolated allowing the activity of structure activity relationship, comparing the activities of monoscharrides and macrocyclic acylation on biological activity. The structures of Mandelalidea A and B are shown in the figure. Cytotoxic activity of mandelalide A was dependent on cell density with actively proliferating tumor cells at low density being actively resistant to the compound. Mandelalides A and B inhibited mitochondrial function and induce caspase dependent apoptotic cell death, due to the inhibition of the mammalian ATP synthase complex V at concentrations of 30-100 nM [33]. Cells with oxidative phenotype, was more likely to be inhibited. Cancer cells can shift their mechanism of ATP production from oxidative phosphorylation to Aerobic glycolysis as nutrients become depleted, causing cell death.

4.4 Mollecarbamates

Mollecarbamates A-D po repeating O-carboxyphenethylamide units and a carbamate moiety. Molleures B-E contains tetra- and penta- repeating carboxyphenethylamide units and a urea bridge in different positions and molledihydroisoquinolone, a cyclic form of O-Carboxyphenethylamide. These metabolites were found to be the only compound known to contain Ortho-carboxyphenethylamide derivatives in their skeleton. None of these compounds produced any antibacterial or antiviral properties [34].

4.5 Palmirolide A

A macrocyclic polyketide isolated from the ascidian *Synoicum adareanum*. Palmirolide A displays selective cytotoxicity towards melanoma by inhibiting V-ATPase [35].

4.6 Phosphoeleganin

A novel phosphorylated polyketide isolated from ascidian *Sidnyum elegans* [36]. It has no sufficient cytotoxic activity against human prostate cancer cells and

human breast cancer cell. It subsequently inhibits the activity of Protein tyrosine phosphatase 1B [37].

5. Polyketides from ascidian associated microbes

5.1 Patellazoles

Patellazoles A-C (**Figure 3**) are a family of compounds produced by the alpha-proteobacterium *Candidatus Endolissoclinum faulkneri*, a microbe found in association with the ascidian *Lissoclinum Patella*. It shows cytotoxicity towards HCT 116 cells by inhibiting protein synthesis. It has several functional roles such as arresting of cell cycle at G1/S phases, and induces cell apoptosis [38].

5.2 Cyanobactins biosynthesis

Cyanobactin gene clusters are capable of encoding, two protease genes, A(N-terminal) and G(C-terminal) that are related to patA and patG genes from the patellamide biosynthetic pathway. A precursor peptide gene E being an homolog to patE which directly encodes cyanobactin structure that acts as a substrate for post translational modifications. Cyanobactin gene clusters may also encode homologs of PatD or PatF, denoted as D-protein and F-protein. Includes thiazoline/oxazoline dehydrogenases (responsible for the aromatization of the heterocycles to thiazoles and oxazoles, methyltransferases. This gene was proven to be essential for the synthesis of non-prenylated patellamides. Cyanobactins are classified into different groups based on a correspondence between genotypes and chemotypes.

5.2.1 Biosynthetic pathway

Cyanobactin biosynthesis begins with the precursor E-peptide, which is composed of an N-terminal conserved leader sequence that is recognized by some of the modifying and cleaving enzymes. Cyanobactin genetic cluster may also employ more than one precursor peptide. Genetic cluster may contain upto10 precursor peptide gene. E-peptide that contains the enzyme recognition sequences, 1,4 hypervariable core regions may be present and dictate amino acid backbone of cyanobactins.

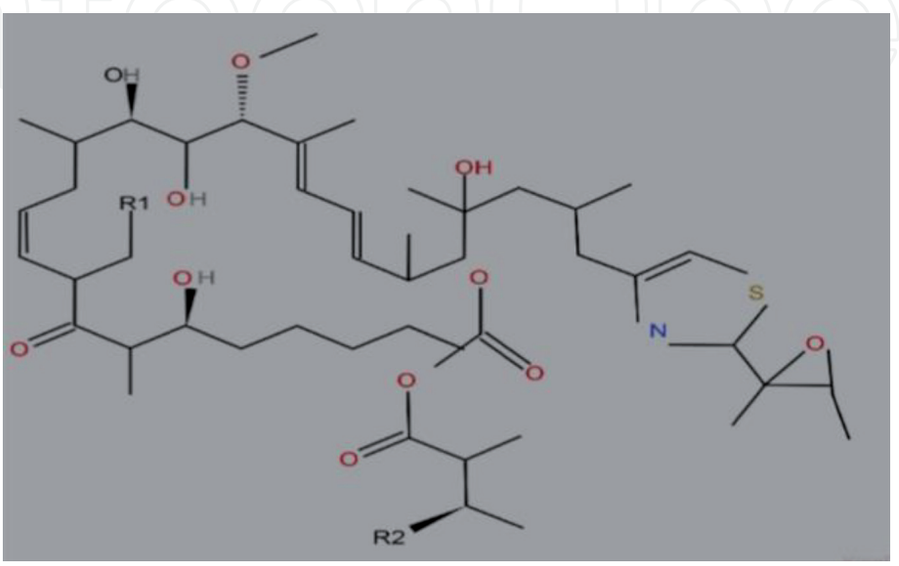

Figure 3.
Structures of Patellazoles A–C [31]. Adapted from Kwan and Schmidt.

Cyanobactins are ribosomally synthesized and post-translationally modifies peptides produced in the ribosome. Biosynthetic enzymes for cyclic peptide synthesis are encoded in the *Prochloron* genome. Precursor peptides are post-translationally modified by various enzymes adding the heterocycles derived from the cysteine, serine and threonine or isoprene units. Modifies peptides are cleaved from the precursor and cyclized to the natural products [39]. These products are capable of exhibiting combinatorial biosynthesis. Ribosomally synthesized and post translationally modified peptides combinatorial chemistry is made mainly because of the core peptide hypervariably, broad substrate [40] specificity, enzyme recognition sequences and modularity of post-translational elements. Many of these post-translational modifications are found in marine organisms. Mechanisms as well as the gene cluster involved in the formation of the thiazoline and oxazoline rings in cyanobactin are well studied. Patellamide pathway, coded by the pat gene cluster which is commomly expressed in *Prochloron* involves several enzymatic steps: Aminoacid heterocyclization, cleavage, peptide cleavage, peptide macrocyclization, heterocycle oxidation and epimerization. Some of the closely related products are also prenylated (**Figure 4(a**, **b**)).

In the presence of D-protein cyclodehydratase, heterocyclization of cysteins, serines or threonines will be directed by sequence recognition. A protease cleaves the precursor peptide RSII, leaving a free amine available for macrocyclization. G-protease splits the precursor peptide RSIII and causes the catalization of C-N macrocyclization. Other transformations may occur such as, prenylation of serine/threonines and tyrosines/tryptophans residues catalyzed by the PatF class of prenyltransferases. Oxidation of heterocycles to oxazoles and thiazoles when oxidized, domain is present within the G gene or separate and geranylation [41].

5.2.2 Heterocyclase

Heterocyclase accompanies heterocyclization of cysteins, serine and threonine residues to thiazolines or oxazolines and eliminates water. Cyanobactins heterocyclases D has been studied in partellamide and trunkamide pathways. Heterocyclases D in both pathways is ATP dependent. An adenylase mechanism has been proposed for TruD, from trunkamide.

An adenylase mechanism has been proposed for TruD, from trunkamide pathway, whose crystal structure presents as the three, domain protein. Enzyme progreesivity requires the presence of a lead protein to be attached to the core, indicating that heterocyclization occurs before cleavage and macrocyclization of the precursor peptide.

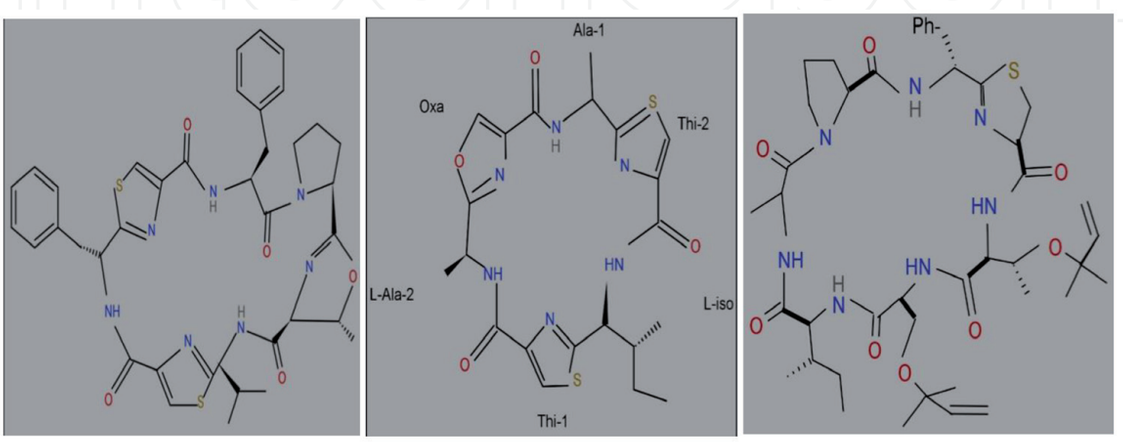

Figure 4.
a)bistratamide M, b) bistratamide N produced from c) Trunkamide A.

The sequence element present in the lead sequence is responsible for heterocyclization. Cyanobactin pathway encoding a heterocyclase modifies a oxidase domain responsible for oxidation of thiazolines and oxazoles to thiazoles and oxazoles.

5.2.3 Macrocyclization

PatA protease from patellamide gene cluster catalyzes the N-terminal protease cleavage from the precursor peptide removing the leader sequence. This reaction catalyzed by the N-terminal protease A and C-terminal protease G, under subtilisin protein family encoded by cyanobactin gene cluster. A kind of protease called PatG isolated from Prochlorom was found to macrocyclize a wide range of synthetic substrates with non-proteinogenic and D-amino acids. Macrocyclase consists of PatG and PagG structural domains representing a catalytic triad. Macrocyclase crystal structure represents a domain of PatG, showing subtilisin folds containing two helices presented by the macrocyclization insert without any change in sequence length. This domain is insensitive to the identity of the residues within the core peptides, as PatG acts on RSIII residues and catalyzes the C-N macrocyclization. During this process, PatA protease removes the amino terminal linked to the core, producing a free amino terminal and PatG protease removes a catalytic terminal flanking the core. Cleaving site is protected by the PatG protease preventing access to water and continues hydrolysis until the transduction reactiobn is completed. PatG emphasizes macrocyclic peptide formation, by removing the C-terminal protease.

5.2.4 Prenylation

Prenylagarmide (pag), trunkamide (tru). Aesturamide (lyn) pathways, encodes the prenyltransferase gene, capable of synthesizing prenylated compounds. Prenyltransferase gene present in patellamide, generates non-prenylated patellamide A and C. Trunkamide contains O-prenylated threonine and serine (**Figure 4**(**c**)). Prenylagarmide contains O-prenylated tyrosine. Prenyltransferase from lyn (LynF) and tru (TruF) pathways. Prenyltransferase from lyn (LynF) and tru (TruF) pathways have been characterized biochemically. However, the reverse O-Prenylated tyrosine undergoes spontaneous claisen rearranging and yieding ortho-substituited phenol. LynF prenylates the oxygen atom of tyrosine residue by using dimethylallylpyrophosphate (DMAPP). TruF prenylates serine and threonine residues on the hydroxyl side chain. PatF from the patellamide pathway, it embraces the other prenyltransferase, classic TIM barrel fold. No enzymatic activity was detected, may be due to absence of prenylation in patellamides A and C. PatF essential for the production of patellamide in vivo and consequently responsible for another function in this pathway. Oxidase domain is conserved among PatG homologs and studies put up a prediction that FMN id dependent. Thiazoline oxidase has been related in sequence to the patellamide enzyme. However its action on microcin pathway was a matter of biochemical study. How this enzyme recognizes the substrate remains unclear, as the microns are linear and patellamides are macrocyclase. One homolog of the oxidase domain of PatG was capable of oxidizing both linear and macrocycle thiazoline containing compounds and another homolog has the ability to perform oxidation on a macrocyclic substrate.

5.2.5 DUF

PatA and PatG proteases contain a domain of unknown function sharing a sequence similarity of about 56%. DUF domains are found in PatA and PatG from the patellamide biosynthetic clusters. Epimerization follows heterocyclization and precedes oxidation. Epimerization is an important role of DUF domain, and its

phenomenon is chemically spontaneous. Crystal structure of PatG-DUF is a novel fold dimer with two zinc ions. Practical importance of the dimer remains unclear since, the residues involved in Zn2+ binding, which is necessary for dimerization are not conserved among DUF domains. DUF domain does not bind to the macrocycle or the core peptide alone.

6. Sulfer containing metabolites

6.1 Polysulfides and alkylsulfides

Sulfur atom rarely found among the marine organism. Ascidians belonging to the genus *Lissoclinum (didemnidae)* had shown resistant towards Plasmodium chemical scaffolds, some of them with unique antiviral activity against mammalian erythrocytes. Among these metabolites, several structurally intriguing antimicrobial polysulfides have activity comparable to the commercially available antimalarials chloroquine and quinine shows activity against bacteria, fungi and other infective agents. Antifungal properties of benzopentathiepin varacin isolated from *L.perforatum*. Due to its antifungal properties, they paved the way for the isolation of.

Lissoclinotoxins A and B. Toxins isolated from *L.vareau* showed activity against *Candida albicans* with a 14 mm zone of inhibition. Polysufides showed an activity of strong cytotoxicity, being 100times more potent than 5 against *Staphylococcus aureus.* Having a minimum inhibitory concentration IC90 of 0.05ug/ml against human colon cancer HCT 116. Role of ascidian associated microorganism, showed activity against *Aeromonas salmonicida* and *Vibrio anguillarium*. Role played by the ascidian associated microorganism in the synthesis and cytotoxic activity was tested against the *Aeromonas salmonicida* and *Vibrio anguillarium* by the zonal inhibition assays of their secondary metabolites reported by the discovery of analogues lissoclinotoxin B. It is a potent inhibitor of bacteria, mainly against the *Aeromonas salmonicidia*. Varacin isolated from the colonial ascidian exhibited antimicrobial properties. It had moderate cytotoxic effects against the Polycitor species. Varacin showed active resistance towards the strain Plasmodium isolated and also exhibited strong activity in vitro against the *Candida albicans*. On the other hand, this peptide exhibited a lower IC 50 value at 296 nM towards the Gram-positive *Bacillus subtilis* [42]. Further, three polysulfites isolated from the colonial ascidian, was isolated as acetates, 4-Trichosporon metagrophytes and it showed resistance to *Candida albicans* with an MIC of 20 and 40 μg/mL.

6.2 Bengacarboline

A beta-carboline alkaloid derived from the ascidian *Didemnin* species, known to contain cytotoxic effect on in vitro A26 human tumor cell line and inhibit topoisomerase II activity [43].

6.3 Ihenyamines A-B

A derivative from the ascidian, *Polycitorella* species containing compounds exhibiting moderate cytotoxicity towards in-vitro cell line studies. Alkaloids of *Staurosporine*, studied on the MONO-MAC-6 cell lines, successfully inhibited the cancer growth and are known to be strong inhibitors of Protein kinase [44]. Pibocin B isolated from the Japan ascidian *Eudistoma* species, has a unique strucrtural species of N-O methylindole alkaloid and known to produce moderate cytotoxic [45] (Makarieva et al.,) effect towards mouse *Ehrlich* carcinoma cells with an ED50 25 μg/mL (**Figure 5**).

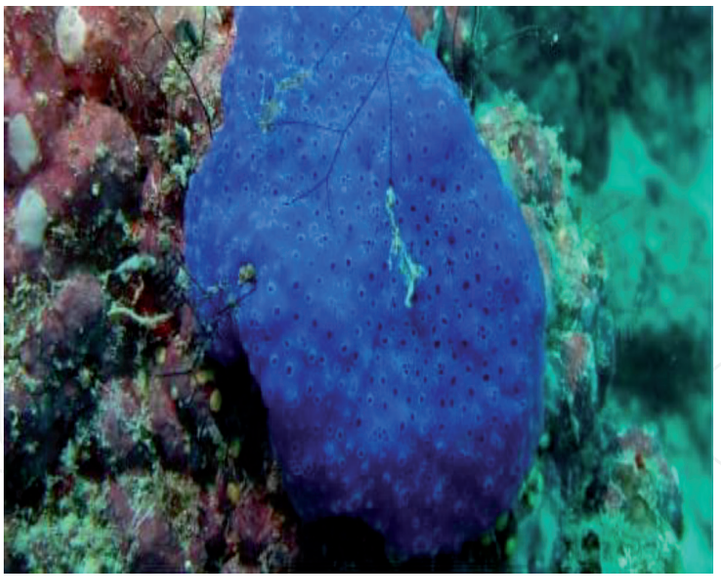

Figure 5.
Showing image of ascidian Eudistoma *species.*

6.4 Shishijimicins A-C

A class of beta-carboline alkaloids, isolated from the ascidian *Didemnum proliferum*. These peptides are potent antitumorigenic agents [46]. Three classes of alkaloids isolated from the Guinea sea squirt *Eudistoma* species consists of Rigidin, RigidinE and 1-methylherbiproline. These three alkaloids were reported to contain moderate inhibitory potential towards human P53 colon carcinoma cell lines and A431 epidermal carcinoma cell lines [47].

An alkaloid Fascaplysin isolated from the sponge *Fascaplysinopsis Bergquist* species, contained an excellent cytotoxic activity against murine C38 CFU cell lines and human H116 cell lines [48]. Meridianins, are brominated 3-(2-aminopyrimidine)-indole alkaloids isolated from the ascidian *Aplidium meridianum.* It is shown to have anti-proliferative effects, inducing apoptosis and inhibiting various cyclin dependent protein kinases, casein kinase-1 and glycogen synthase kinase-3 in NT2 teratocarcinoma cells [49].

6.5 Lamellarin D

This alkaloid represents an excellent cytotoxic effects towards tumor cells and proposed to be an anticancer agent for targeted topoisomerase –I cancer therapy [50]. This series of alkaloids represents an ideal source for developing anti-cancer agents. A few aspects of the various mechanism imposed by the lamellarin analogue, made this peptide to be used in biotechnology and pharmaceutical industries [51] (Marco et al.,).

Schupp and his co-workers reported alkaloids of Staurosporine and their eight subderivative alkaloids analogues such as 3-hydroxystaurosporine, 4-N-demethylstaurosporine, 3-demethoxy-3-hydroxylstaurosporine, 3-hydroxy-3-demethoxy-3-hydroxystaurosporine, 11-hydroy-4-N-demethylstaurosporine, 11-hydroxystaurosporine, 4-N-methylstaurosporine, 3-hydroxystaurosporine. These alkaloids were isolated from *Eudistoma toealensis*, a colonial ascidian and its alkaloids are being used in biotechnology and pharmaceutical industries.

6.6 Somocystinamide A

A lipopeptide isolated from *Lyngbya majuscula* (**Figure 6**), showed potent cytotoxic activity against N2A cells. It was found to be an potent apoptosis inducer

Figure 6.
Image showing ascidian Lyngbya majuscula.

towards a number of cell lines, activation of caspase 8 and angiogenic endothelial cells via intrinsic and extrinsic pathways.

6.7 Apratoxin A

A cyclodepsipeptide isolated from ascidian, *Lyngbya majuscula* showed antiproliferative activity in KB and LoVo cancer cells. It induces the antiproliferative activity through the induction of G1 cell cycle arrest, apoptotic cascade and partially initiated by antagonism of FGF signaling via STAT3 [52].

7. Cyanobacteria

Cyanobacteria, known as blue-green algae, are ancient photosynthetic prokaryotes which inhabit a wide diversity of habitats including tropical reefs, fresh water ponds, streams and puddles and fresh water ponds. Luxuriant growth of cyanobacteria in these adverse environments conditions is based on their abilities of forming resistant spores, opportunistically colonizing micro-habitants and surviving under conditions of high UV-flux through production of UV-absorbing pigments, has made them one of the successful life forms on earth. Cyanobacteria associated with ascidians, their symbotic relationship was first found out in 1982 by Kott.

Cyanobacteria are phylum of bacteria that produce oxygen during photosynthesis. Host ascidians that exhibit symbiotic relationship with cyanobacteria, Prochloron, which belong to the Didemidae family and are therefore called as "Didemnin ascidians". Cyanobacterial symbionts can both provide nutrients by means of Carbon fixation, nitrogen recycling and metabolite production and also exhibits defensive reaction for the host ascidian. Ascidian host are capable of producing some of the nitrogen containing nutrients that are needed for the cyanobacterial symbionts growth and also protection against the ultra violet radiation. Additional feature is that, a rich source of biologically active products, has assisted some of these organism to survive in predator-rich tropical reef ecosystems. Tropical marine Cyanobacteria particularly the filamentous forms such as *Lyngbya* species or *Symploca* species have been a source of novel natural products with therapeutic and biotechnological potential. Marine cyanobacteria are considered to be an important source of structurally diverse and biologically active natural products. Different peptides isolated from a wide variety of marine cyanobacteria, induces

anticancer effects on various human cell lines. Most studied cytotoxic cyanobacteria on human tumor cell lines inducing minimal inhibitory effects [53].

Cyanobateria have a rich complement of photosynthetic pigments, including chlorophyll a and b, as well as several accessory pigments (phycoerythrin, phycocyanin, and allophycocyanin). Phycoerythrin has found application in biotechnology as a conjugate to antibiotics that then allow visualization of cellular constituents and processes and chlorophyll is being explored for its cancer chemotherapeutic activity. Apratoxin A is a cyclic depsipeptide extracted from *Lyngbya majuscule*. Exhibited cytotoxic effects on Human HeLa cervical carcinoma cells by cell cycle inhibition [54]. Similar mechanism was also reported on cyclic depsipeptide Coibamide A, isolated from *Leptolyngbya* species on Human lung cancer cell line and Lyngbyabellin B isolated from *Lyngbya majuscule* on Human Burkitt [55] lymphoma cells. Dolastatin 10 and Symplostatin 1, isolated from *Symploca* species, showed cytotoxic effect on human lung cancer cell line and Human breast carcinoma cell line by both Bcl-2 phosphorylation and Caspase-3 protein activation. Anticancer peptides such as *Lyngbya sp* and *Nostoc sp*, shows activity against cancer on different cell lines through microfilament disruption, secretory pathway inhibition.

Cyanobacteria inhibit Gram-negative and Gram-positive pathogenic bacterial species. Extracts of *Cylindrospermopsis raciborskii*, CYP011K and *Nostoc* species,

CENA69 possibly caused cancer cell inhibition. Extracts from *Fischerella* species, CENA213 showed inhibition of 3LL lung cancer cells. NPLJ-4 extracts isolated from *M.aeruginosa* reported to have inhibition against CT26 colon cancer cells. All of these extracts are prone to have low inhibitory activity towards human peripheral blood lymphocytes.

Aphanazomenon flos-aquae, freshwater cyanobacteria reported to contain immune stimulating properties, Other cyanobacteria Spirulina, a rich source of digestable proteins with a complete complement of essential amino acids [56].

Lyngbya majuscule from Curacao, yielded metabolites with broad biological properties, including those with toxicity to arthropods, those toxic to fish and those toxic to gastropods.

Bisanthrantaquinones, isolated from blue green algae associated with the colonial ascidian *Ecteinascidia turbinate*. These are the antimicrobial metabolites from ascidian-associated cyanobacteria (**Figure 7**), available to date. It has greater antibacterial effectiveness, and has resistance towards multi-drug resistant bacteria and vancomycin-resistant *Enterococcus faecalis* with an MIC of 0.6 and 12uM [57].

Cyanobacteria are considered to be an important source of bioactive metabolites, with various aspects of cytotoxic, antiviral, anticancer, antimitotic, antimicrobial, specific enzyme inhibitor and immunosuppressive activity. Cyanobacteria holds the presence of non-ribosomal peptide synthetase and polyketide synthetase genes, owing it to be the potential for finding novel natural drug products from these organism. Thus, cyanobacterium species are a rich strain enriched with the source of natural products with potential for pharmacological and biotechnological applications.

7.1 Tubulin binding proteins

Microtubules play many significant roles in cell biology. Formation of microtubules results from the polymerization of the subunit protein tubulin, first into heterodimers subsequently binds end to end with other heterodimer forming a protofilament, which in turn interacts to form sheets and eventually microtubules. Specifically, assembly and motility are crucially for the formation of the spindle apparatus during cell replication and mitosis where microtubule fibers direct the separation of sister chromatids into the resulting daughter cells. In case of rapidly

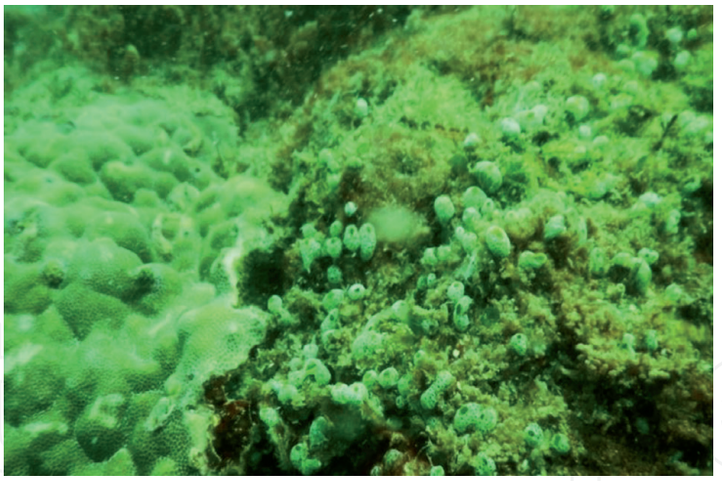

Figure 7.
Image showing marine cyanobacteria.

dividing cancer cells, microtubule assembly has been an important target in the development of new chemotherapeutic agents. Various drugs have developed to disrupt the process of mitosis and cause catastrophic cell death by either stabilizing microtubule complexes, caused by taxol. Depolymerization of the tubulin protein complex caused by Vinblastin [58]. Recently antimicrobial peptides targeting intracellular tubulin has developed from marine natural products.

Pharmacological properties of the marine mollusk, derivatives of *Aplysiidae* commonly know as the 'sea hare' or 'nudibrunch' has been reported for their toxic secretions. Biological activity of the cyanobacteria present in sea hare *Dolabella auricularia*, its structure consists of an active constituent, dolastatin 10. Dolastatin 10 displayed exceptional activity against the P388 lymphocytic leukemia cell line with ED50 value of about 4.6*10-5 g/ml. It is also reported to have potent antineoplastic activity. Dolastatin 10 isolated from field collections of the marine cyanobacterim *Symploca* species, clarifying the concept that the true biosynthetic source is the cyanobacteria and not the sea hare. Dolastatin 10, a unique linear pentapeptide is composed of four novel amino acid residues such as dolavaline, dolaisoleucine, dolaproline, dolaphenine and valine. High resolution mass spectroscopic analysis such as 1H (COSY, 2D-J resolved) and 13C NMR methodologies revealed the structure of this linear pentapeptide. This peptide sequence was assigned on the basis of several low resolution mass spectral fragmentation techniques. This peptide was found to be involved in the binding of Dolastatin 10, whereas other antimicrobial peptides near the exchangeable nucleotide and vinca alkaloid sites on microtubules [59]. Dolastatin 10 inhibits microtubule assembly in vitro and subsequently blocks cytokinesis. Also this peptide was noted for its non-competitive inhibition of radiolabeled vinblastine and vincristine to tubulin as well as tubulin dependent hydrolysis of GTP.

Dolastatin 10 binds to the 'peptide groove' lying within the r- subunit of tubulin. Molecular modeling suggested that the chiral centers of dolavaline, valine and dolaisoleucine binds in a manner that require the dolaphenine moiety to sterically block access to the vinca alkaloid and exchangeable nucleotide binding sites. Evidence of noncompetitive inhibition of Vinca alkaloid binding was realized by observation that tubulin polymerization and nucleotide binding are substantially diminished at sub-stoichiometric concentrations of dolastatin 10.

Dolastatin 10, on its Phase II clinical trial proved to be an antitumor agent, by evaluating its antitumor efficacy in patients with measurable recurrences of platinum –sensitive ovarian carcinoma in relation to the degree of toxicity [60].

7.2 Dolastatin 15

Dolabella auricularia, cyanobacteria associated sea hare contained another cytotoxic peptide called as dolastatin 15 (**Figure 8**). It was discovered by the process of bioassays guided fractionation and purified it as a minor fraction of about 6.2 mg from 1600 kg of wet sea hare. It was evident that this compound is well associated with the sea hare from its cyanobacterial diet. Dolastatin 15 is a linear heptadepsipeptide composed of the dolavaline (N,N- dimethyl valine), valine, N-Me-valine, proline (x2), 2-hydroxyisovaleric acid. New Dpy moiety present in this peptide was proposed to be originated biosynthetically from the N-acetyl-phenyalanine methyl ester by intramolecular condensation. This peptide showed specific activity towards the P388 lymphocyte leukemia cell line of the national cancer institute (NCI) [61]. Dolastatin 15 was found to bind in the Vinca alkaloid domain of the tubulin complex, a definitive binding site was not identified. On the other hand, this peptide was shown to weakly bind tubulin with concurrent weak inhibition of crytptophyccin 1 binding, its specific acts are still unclear. Further on going work could determine the molecular mechanism of dolastatin 15 activity, although it has been stopped to enter the preclinical trials due to its general toxicity.

7.3 Actin binding proteins

Actin cytoskeleton is a dynamic network of filaments, which is associated with several proteins, plays an important role in cell shape, motility and signal transduction, this further switches on the other processes like embryonic development, tissue repair, immune response and tumor formation. However in cancer biology, actin cytoskeleton and actin associated proteins undergo modification in transformed tumor cell and impose ability to adhere and metastasize. It can be used for developing new chemotherapeutic agents. Actin targeting molecules could disrupt actin by destabilizing the filaments or induce hyperpolymerization [62].

7.4 Hectochlorin

Marine cyanobacteria *Lyngbya majuscula* provided a suitable source for the isolation of Hectochlorin. It was a potent antifungal agent. It showed activity towards

Figure 8.
Image showing Dolabella auricularia.

the Ptk2 cells derived from *Potorous tridactylus*, when treated with hectochlorin showed an increase in the number of the binucleated cells as a result of arresting the cytokinesis process. This peptide is very similar in action to jasplakinolode, in promoting hyperpolymerization of actin. Main difference that lies in between hectochlorin and jasplakinolode is that former can displace fluorescently labeled phalloidin from actin polymers, while the latter have two distinct interactions with actin. Hectochlorin, also strong potential towards the cell lines in the colon, melanoma, ovarian and renal sub-panels [63]. It showed a flat response curve against most cell lines, a specific activity of the compounds that are anti-proliferative but not directly cytotoxic [60].

7.5 Lyngbyabellins

This specific peptide was isolated from *Lyngbya majuscula* from south pacific and Caribbean and bear suitable structural resemblances to hectochlorin and dolabellin. Structural of lyngbyabellin A was determined using 2D NMR techniques and its absolute stereochemistry was determined by the chiral HPLC analysis. Lyngbyabellin A exhibited IC50 value of 0.03 μg/mL and 0.50 μg/mL against KB cells (human nasopharyngeal carcinoma cell line) and LoVo cells (human colon adenocarcinoma cells). It also disrupt the microfilament network in fibroblastic A10 cells at 0.01–5.0 μg/mL [64]. At higher concentrations of Lyngbyabellin A many cells became binucleate, an observation which inhibits cytokinesis. Lyngbyabellin B was found to be less toxic than lyngbyabellin A with IC 50 value of 0.10 μg/mL. It produces the same effects as hectochlorin on PtK2 cells, increase in number of binucleate cells were observed, when 10 M of the agent was treated with the cells. This finding proposed that actin is the main cellular target of the lyngbyabellins.

8. Neurotoxic compounds

8.1 Antillatoxin

Lyngbya majuscula served as the source for the extraction of the crude extract of Curacao, found to be highly ichthyotoxic and molluscicidal. This extract was then fractionation and subsequent purification led to the finding of the potent lipopeptide ichthyotoxin, antillatoxin. Antillatoxin is one of the most ichthyotoxic metabolites isolated from a marine cyanobacterium with an LD50 value of 0.05 g/mL. Pharmacological studies showed that the antillatoxin was neurotoxic and rapidly morphologically changes in rat cerebellar granule neurons (CGC's), also includes bebling of neurite membranes. Toxic effects of Antillatoxin was remarkably reduced, when the cells were treated with NMDA receptor antagonists like dextrophan [65]. Thus, its toxic effects were mediating by NMDA receptor dependent mechanism. Antillatoxin shown to be a powerful activator of voltage gated sodium channels and resembled brevetoxin. Unique biological activity of antillatoxin was mainly combined with its structure [66].

8.2 Antillatoxin

A lipopeptide isolated from *Lyngbya majuscula*, which is closely related to the antillatoxin with a larger B-methyl homophenylalanine instead of N-methyl valine residues was termed as Antillatoxin B. It is collectively found to be similar to ichthyotoxic (LC 50 = 1.0 M) and a potent activator of voltage gated sodium channels in mouse neuroblastoma cells [67].

8.3 Cyanobacterial metabolites

8.3.1 Barmamide

Isolated from the lipid extract of *Lyngbya majuscula* and consists of specific elements such as trichloromethyl group. Bioassays predicted that barbamide possesing anti-molluscicidal activity (LC 50 = 10.0 μg/mL) [68]. Whereas was found to be inactive in other assays and its biological properties still remains unknown.

8.3.2 Botryllus schlosseri

A specific bacterial species associated with *Botryllus schlosseri* was isolated and tested for their specific biological activities. *Bortyllus schlosseri* is a colonial ascidian composed of several tiny individual zooids enveloped by single tunic. Its an native to Europe. MTT analysis performed confirmed the cytotoxic activity of the crude extracts of the isolated bacterial strains. Extracts showed that, about 90% of the extracts showed cytotoxicity towards human heptatocellular carcinoma Bcl 7402 cells and human cervical carcinoma cell lines HeLa. Antimicrobial activity of the ascidian *Botryllus schlosseri* associated bacterial extracts showed that, it inhibits Gram-negative bacteria, Gram-positive bacteria, human pathogenic fungi and aquatic animal pathogenic bacteria. Thus, it exhibited higher incidence of resistance towards Gram-positive bacteria such as *Bacillus subtilis* and *Staphylococcus aureus* than Gram-negative bacteria [69].

9. Symbiotic organisms

Symbiotic bacteria contribute secondary metabolites necessary for defense and the survival of ascidians. About 80 percent of the currently available secondary metabolites obtained from ascidians were made only by its symbiotic bacteria. These metabolites are essential for the interaction between the host and symbiont and the bacteria are phylogenetically diverse [70].

9.1 Callynormine A

This peptide represents a new class of heterodetic cyclic peptides possessing an –amido-aminoacrylamide cyclization functionality. Cyclic endiamino peptides composed of a Hyp part [71], which is likely to be present in its peptides such as callynormine A and callyaerin A-D.

9.2 Gombamide A

A cyclothiopeptide consisting of an unusual amino acid residues like pHSA and pyroGlu [72]. It possess moderate inhibitory action towards the, Na+/K+-ATPase.

A specific new class of proline rich cycloheptapeptides derived from the photooxidation of tryptophan consisting of cytotoxic phakellistatin 3 and isophakellistatin 3. This peptides has an unusual amino acid residue such as “Hpi” respectively. These proline rich peptides act in a very divergent way, capable of causing stereospecific interaction with the membrane system. These interactions are caused by the intracellular targeting, compared to the general membrane disruption mode of action of the conventional antimicrobial peptides. It was found that proline rich antimicrobial peptides stereo specifically binds the intracellular foreign particles, such as the bacterial heat shock proteins DnaK. These peptides have a good water solubility, high potential for killing bacteria and lower cytotoxic

activity at higher concentrations, these factors contribute to the development of the novel antimicrobial therapeutic agents in the field of medicine [73].

These peptides could easily enter the bacterial cell, binding and disrupting specific targets such as ribosome, thereby inhibiting protein synthesis. However all these factors, concludes that these peptides could subsequently be used as molecular hooks, for identifying intracellular or membrane proteins involved in this mechanism of action [74]. And it could be used for specifically altering novel therapeutics for drug delivery.

Scleritodermin A causes inhibition of tubulin polymerization [75].

Immunosuppressive activity of cyclolinopeptide A results from the formation of complex with cyclophilin and causing inhibition of phosphatase activity of calcineurin, plays an important role in T-lymphocyte signaling [76].

Cemadotin, a water soluble synthetic component of linear peptide dolastatin 15, which is reported to act on microtubules and causing strong suppression of microtubule dynamics [77].

9.3 Didemnin B

A cyclic depsipeptide derived from the marine cyclopolypeptide undergo clinical trials because of its potential to target oncological patients. Its high toxicity, poor solubility and shorter life span led to the discontinuation of didemnin B in clinical trials [78].

Didemnin B, belonging to a class of heterodetic non-polar cyclic peptide associated with several Antiviral, antitumor, immunomodulating properties, potency inhibits protein and DNA synthesis by binding to eukaryotic translation elongation factor EF-1 in a GTP dependent manner. Formation of the [79] Didemnin B-GTP-EF-1 complex could be responsible for protein synthesis inhibition.

Inhibition of protein synthesis by didemnin B occurs by stabilization of aminoacyl-tRNA to the ribosomal A-site, preventing the translocation of phenylalanyl–tRNA from the A- to the P-site, preventing peptide bond formation.

Tamandarin A acts in a very same mechanism as didemnin B. Aplidine's involves several mechanism of action such as cell cycle arrest and protein synthesis inhibition. It induces early oxidative stress and results in a rapid activation of JNK and p38 MAPK phosphorylation by activating both kinases occurring among before the activation of apoptosis [80].

Didemnin B causes the death of several transformed cells through apoptosis, DNA fragmentation within the cytosol and generation of DNA ladders [81].

A linear depsipeptide kahalalide F, has predominant antifungal and antitumor activity, and underway in clinical trials.

A cyclic depsipeptide Plitidepsin (dehydrodedemnin B or aplidine) is in its clinical trial for being developing it as a drug. In 2003, plitidepsin was given orphan drug status for treating acute lymphoblastic leukemia. In 2007, it underwent phase II clinical trials and in 2006 it is announced for small phase-I clinical trials for treating multiple myeloma [82].

Antimitotic dolastatins group, dolastatin 10 and 15 are undergoing phase-II clinical trials. A synthetic analogue of dolastatin 15, cemadotin is also in phase-II clinical trials for its promising cancer chemotherapeutic agent.

9.4 Ecteinascidian—743

A specific alkaloid isolated from the tunicate *Ecteinascidia turbinate*, represents a rich source of symbionts whose aqueous extract are known to contain anticancerous agents. Ecteinascidin alkaloids molecular structures are known to be defined as

complex tetrahydroisoquinolones. This alkaloid is a major meatabolite possessing cytotoxic activity against leukemia cells (IC 50 0.5 ng/mL). Ecteinascidins structure is considered to be of a natural microbial origin (eg saframycins) [83]. This alkaloid because of its stability and relatively high natural abundance made it most suitable for entering clinical trials. Ecteinascidians-743, entered phase-I clinical trials after rendering, to have an higher therapeutic index and potency. Recently, it was found that ET-743binds to the minor groove of DNA to induce a bend in the DNA helix towards the major groove. ET-743 plays an important role in causing interference with the cellular transcription coupled nucleotide excision repair to induce cell death and cytotoxicity which is independent of p53 status. However, advanced ovarian, breast and mesenchymal tumors showed more response to ET-743 in phase-I clinical trials. ET-743 in phase-II clinical trials showed more heightened response towards soft tissue sarcoma (STS), ovarian and breast cancer. There are two patents for bacterial symbionts of the tunicate *Ecteinascidia turbinata*, primary focus was on the isolation of the producing microbe, secondary one uses 16S rDNA sequences to identify the endosymbiont as *Endoecteinascidia frumentensis*, the source for producing the ecteinascidins [84].

9.5 Helichondrin B

A complex polyether derived from the marine animals such as sponges, tunicates and their various predators. Compounds such as palytoxin, maitotoxin and halichondrins, because of their potential even very small quantities of these compounds could aid valuable commercial sense. Halichondrins was first isolated from the Japanese sponge *Halichondrin okadai* (Uemura). Halichondrin B and several natural analogs were subsequently been derived from various sponges such as, *Lissodendoryx* species, *Phakellia carteri* and *Axinella* species, thus it strongly suggest that this type may be constructed by an ascidian associated microorganism. A number of studies reported their cell toxicity, and it was found that halichondrins are tubulin inhibitors, non-compatitively binding to the vinca binding site and causing a charateristics G2-M cell cycle arrest by concomitant disruption of the mitotic spindle. *Dysidea herbacea*, a sponge and its symbiotic cyanobacterium *Oscillatoria spongellae*. These cyanobacterial cells are known to contain a series of highly distinctive chlorinated peptides, which has strong structural precedence in metabolites isolated from the free-living cyanobacterium *Lyngbya majusculea*. However a similar peptide from tunicate *Lissoclinum patella*, harbors an abundance of cyanobacterium *Prochloron* species which produces a series of distinctive cyclic peptides, associated with both cyanobacterial and tunicate cells. Palytoxin and maitotoxin are both available as research biochemicals [85].

9.6 C-Phycocyanin

A blue green pigment-protein complex isolated from the marine cyanobacteria *Agmenellum quadruplicatum, Mastigoclaudus laminosus*. This pigment appeared to be an activator of pro-apoptotic gene and also the down regulator of anti-apoptotic gene expressions [86]. Its activity of apoptosis on HeLa cell lines in-vitro, resulted from the transduction of apoptosis signals. These apoptosis further leads to the path of cell shrinkage, membrane bebbing, nuclear condensation and DNA fragment known to be observed from A549 and HT29 treated with C-phycocyanin.

10. Conclusion

However, a handful of antimicrobial peptides have found to be approved today for clinical use as anti-infectives. Cyclic peptides such as gramicidins and

polymyxins are well characterized. Gramicidins are used in treating infections such as infection of the surface wounds as well as the infections of nasal, ocular and throat infections. On the other hand polymyxins are used for treating eye infections prior to local administration and for selective decontamination of the digestive tract and also for systemic infections caused by drug-resistant gram-negative pathogens. Daptomycin, a cyclic antimicrobial peptides in clinical practice to treat skin complications and skin-structure infections caused by Gram-positive bacteria mostly, *Staphylococcus aureus*. Omiganan, a 12 amino acid analog of indolicidin, has been incorporated in the local treatment of Catheter related infections, atopic dermatitis, genital warts, acne vulgaris. Pexiganan, a 22 amino acid analog being evaluated in the Phase III clinical trials for the treatment of mild diabetic foot ulcers, burns and decubitus ulcers. PXL01, iron-binding lactoferritin present in milk and mucosal secretions, evaluated in phase II clinical trials for treating post-operative adhesions in patients undergoing flexor tendon repair surgery of the hands [87].

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