Mode of action of ascidians: A new gateway in the era of anticancerous activity

Jain Seema Sachin
Department of Biotechnology, Shree Ramkrishna Institute of Computer Education & Applied Sciences, Veer Narmad South Gujarat University, Surat, Gujarat, India

Marjadi Darshan Sunil
Department of Biotechnology, Shree Ramkrishna Institute of Computer Education & Applied Sciences, Veer Narmad South Gujarat University Surat, Gujarat, India

ABSTRACT

Ascidians (tunicates) are invertebrate chordates, and prolific producers of a wide variety of biologically active secondary metabolites from cyclic peptides to aromatic alkaloids. Several of these compounds have properties which make them candidates for potential new drugs to treat diseases such as cancer. Among the first six marine derived compounds that have reached clinical trials as antitumor agents, three are derived from ascidians, evidence of the high potential of these organisms as a new source of antitumor compounds. Cancer is a complex disease involving cell transformation, dysregulation of apop.tosis, proliferation, invasion, angiogenesis and metastasis. Indeed, ascidian-derived natural products have yielded promising drug leads, among which ecteinascidin 743 (Yondelis®) and dehydrodidemnin B (Aplidin®) are in clinical usage for the treatment of specific cancers. Treatment for cancer does not have potent medicine as the currently available drugs are causing side effects in some instances. New drugs with milder side effects are needed to replace and improve existing medicine. In this context, the natural products derived from marine organisms have gained significance. The current study aims at evaluating anticancer activity of ascidians against various cell lines and mode of action of compounds obtained from ascidians.

Keywords: Ascidians, Secondary metabolites, Bacterial symbiosis, anticancer activity, Mechanism of action, Marine Natural Product

1. INTRODUCTION

Ascidians (urochordates, tunicates), commonly known as sea-squirts, belong to the Phylum, Chordata; sub-phylum; Tunicata; class, Ascidiacea. Ascidians are exclusively marine, abundant in harbors, and can be found all over the world from near the surface to great depths. The three orders within the class Ascidiacea, based on the structure of the adult branchial sac, are Aplousobranchia (almost exclusively colonial), Phlebobranchia, and Stolidobranchia (in both solitary and colonial forms. . Ascidians, along with sponges and bryozoans, produce a rich variety of secondary metabolites presumably to avoid predation and as an anti-fouling mechanism. Anti-cancer drugs are the main area of interest in the screening of Marine Natural Products from ascidians (64%), followed by anti-malarial (6%) and remaining others. FDA approved ascidian compounds mechanism of action along with other compounds status of clinical trials (phase 1 to phase 3) are discussed here in.. These include cyclic peptides and depsipeptides and many different types of aromatic alkaloids essential for the interaction between host and symbiont, and the bacteria are phylogenetically diverse . Many of these metabolites are not produced by the ascidian themselves but by endosymbiotic micro-organisms. Symbiotic bacteria contribute secondary metabolites necessary for defense and the survival of ascidian. About 80 of the currently known secondary metabolites from ascidians are made by symbiotic bacteria .

There are over 3000 species of ascidians worldwide and in India ratio is 434. Till date only 5% of living ascidian species were studied from <3000 species. Many can tolerate and accumulate heavy metals, although these metals affect the development of embryos and larvae in a dose-dependent fashion. This makes certain species of ascidians useful as indicators of water quality in bioassays for pollutants. In addition, ascidians embryos are also useful as a model to study the neurodevelopment toxicity of different compound. Several families of ascidians accumulate very high levels of vanadium (up to 350 NM) in tissues and blood cells called vanadocytes. These include cyclic peptides and depsipeptides and many different types of aromatic alkaloids.

2. METHOD

In India major scientist those are involved in finding tunicates anticancerous activity are VK meenakshi and et al. Dr abdul Jaffar et al from Tamilnadu is also involved in their studies, they find barcode for different gene and identify the animal. All work in India is done on tunicates collected from South coast of India nothing has been done from any other coast. There is plenty of scope of work which could be done from Okha (Gujarat), in which many tunicates are found in ample amount. The physiological function of the accumulated vanadium is presently unclear. It has been suggested that it may be involved in chemical defence. Ascidians are important ecologically due to their invasive potential and adverse effects on native fauna and aquaculture. Fractions were assayed for antitumor and apoptosis inducing properties, revealing many molecules with potential awaiting further research.

During 2005 and 2006, marine pharmacology research directed towards the discovery and development of novel antitumor agents was reported in 171 peer-reviewed articles. The organisms yielding these bioactive marine compounds included invertebrate animals, algae, fungi and bacteria. Antitumor pharmacological studies were conducted with Noteworthy is the fact that marine anticancer research was sustained by a global collaborative effort, involving researchers from Australia, Belgium, Benin, Brazil, Canada, China, Egypt, France, Germany, India, Indonesia, Italy, Japan, Mexico, the Netherlands, New Zealand, Panama, the Philippines, Slovenia, South Korea, Spain, Sweden, Taiwan, Thailand, United Kingdom(UK) and the United States of America.

Ascidians have provided a treasure trove of interesting biologically active compounds and much progress has been made in recent years. There are several major challenges in the pipeline from natural product discovery to therapeutic drugs, including the need for sufficient supply of compounds and a lack of knowledge of the biosynthetic pathways or even the responsible organism (symbiotic bacterium or host ascidian) and mechanism of action. Taxonomic identification of ascidians by morphology is also a problem, due to the shortage of expert taxonomists. This can be overcome with DNA barcoding, recently applied to *Lissoclinum fragile* and four Indian ascidians by sequencing a short segment of mitochondrial DNA coding for subunit 1 of cytochrome C oxidase [1]

There is a list of scientists those are working on different ascidian and extracted different compound out of them.

Table (1): Ascidians Species along with their compound and effects

Scientist	Ascidian Species	Effect	Compound	Reference
V.K Meenakshi et al	Phallusia Nigra Savigny,	Administration of the extract of Phallusia nigra decreased the weight, volume of the tumor and increased the percentage inhibition. An increase on median survival time, percentage of life span, non viable cells and decrease in packed cell volume.	2-Piperidinone, Benzeneacetamide, Tetradecanoic acid, n-Hexadecanoic acid, Phenol 3-pentadecyl, (Z,Z,Z)- phenylmethyl ester of 6,9,12-Octadecatrienoic acid, (z)-phenylmethyl ester of 9-Octadecenoic acid, Cholesterol, Cholestan-3-ol and 3-hydroxy-(3a,17a)-Spiro [androst5-ene-17,l'-cyclobutan]-2'-one	[2]
V.K Meenakshi	Ecteinascidia venui Meenakshi	Treatment with ethanolic extract of Ecteinascidia venui showed a decrease in tumour volume, packed, viable cells and increase in median survival time, life span and nonviable cells of S-180 tumour	1-(2-Ethyl-3-cyclohexenyl)ethanol, (E,E)-methyl ester of 9,12-Octadecadienoic acid, (E)-methyl ester of 9-Dodecenoic acid, 9-Octadecenal, (Z)6,(Z)9-Pentadecadien-1- ol, (Z,Z)-9,12-Octadecadien-1-ol,13-methyl-Oxacyclotetradecane-2,11-dione, Eicosane, Tetradecyloxirane, (R)-(-)-14-Methyl-8-hexadecyn-1-ol, Nonadecane, 1-Iodo-2-	[3],[4]

			methylundecane.	
V.K Meenakshi	Microcosmus exasperatus	Antitumor and immunomodulatory activity of the ethanolic extract of the simple ascidian Microcosmus exasperatus was assessed against Dalton's Lymphoma Ascites (DLA) cells. 100% toxicity was observed at a concentration of 0.80 mg/ml. The extract at 50, 100, 150	n-hexadecanoic acid (21.66%), tetradecanoic acid (18.98%), trichloroacetic acid, hexadecyl ester (12.57%), 26-Nor-5-cholesten-3á-ol-25-one (10.70%), 6,9,12-Octadecatrienoic acid, phenylmethyl ester, (Z,Z,Z)- (8.29%), Cholestan-3-ol (6.95%) and 2-piperidinone, N-[4,bromo-n-butyl]- (3.48%)	[5]
Satheesh Kumar Palanisamy et al	Phallusia Spp	The extract of p. Nigra showed anti tumor activity against HT29 colon cancer and MCF7 breast cancer compared to P. Arabica.	46 metabolite peaks containing between 234 and 860 *m/z* in *P. arabica* extract and 68 metabolite peaks containing between 170 and 870 *m/z* in *P. nigra* extract were reported.	[6]
Divya T Dharan et al	Aplidiam Multiplicatum	A. multiplicatum contains various bioactive compounds in ethanolic extract with various activities like antimicrobial, anti-cancer, diuretic, anti- inflammatory, anti-fungal, antioxidant	Prevailing compounds are 4-Butylbenzoic acid, tridec-2-ynyl ester (41.7%), 5,8,11,14,17-Eicosapentaenoic acid, meth (20.8%), Pyrrolo [1,2-a] pyrazine-1,4-dione, hexahy (13.6%), Phenol, 3,5- dimethoxy-, acetate(10.0%), Vinylbital (8.3%), 4- and Methylimidazole-5-[1,1-dimethylethanol (6.0%)	[7]
Satheesh Kumar Palanisamy et al	Styela plicata	S. plicata shows antitumour activity against four tumour cell line. Hela, HT29, MCF-7 and M14	Total 71 metabolites peaks with containg 105 and 1365 m/z in S. Plicata.	[8]

Table (2): Successful ascidian marine peptides in clinical development

Compound Name	**NP or derivative**	**Origin NP collected source organism**	**Disease Area**	**Clinical status**	**Company/ institution/**	**Reference**
Lurbinectedin	Natural product	Ecteinascidins/tunicte	Cancer	Phase II	PharmaMar(colenar Viejo, Madrid, Spain)	[9]
Plitidepsin	Natural product	Aplidium albicans	Cancer	Phase II& III	PharmaMar(colenar Viejo, Madrid, Spain)	[10]
DidemninB	Natural product	Tridemnum solidum	Cancer	Phase III(hold)		[11]

Table (3): Peptides derived from marine ascidians with possible therapeutic applications

Sr no	**Peptide**	**Type of peptide**	**Species**	**Possible application**	**Reference**
1	Aplidine	cyclodespsipeptide	Aplidium ablicans	Antitumour anti leukemic	[12]
2	Trunkamide A	Thaiazoline cyclopeptide	Lissoclinum patella	Antitumour	[13]
3	Didemnin B	Depsipeptides	Tridemnum Solidum	Antitumour, antiviral immunosuppresssive activities	[14]
4	Lissoclinamides	Cyclic peptide	Lissoclinum patella	Antineoplastic, human fibroblast, bladder carcinoma	[15]
5	Styelin D	Cytotoxic peptide	Styela clava	Gram negative and gram positive bacteria	[16]

Table (4): Ascidians toxins and their mode of action

Sr No	Compound	Ascidian source	Compound Class	Biological Activity	Reference
1	Ascididemin	Didemnum spp	Pyridoacridine alkaloid	Cytotoxic	[17, 18]
2	Bistamides	Lissclinum Bistratum	Spiroketal	Cytotoxic,induces protein phosphorylation	[19-23]
3	Bistratamides	Lissclinum Bistratum	Cynobactins	Cytotoxic, metal binding	[24]
4	Botryllamides	Botryllus sp.	Brominated tyrosine derivatives	MDR reversal	[25, 26]
5	Diazonamide A	Diazona angulata	Cyclic peptide	Cytotoxic	[27-29]
6	Eudistidines	Eudistoma sp.	Novel alkaloids	Inhibition of protein protein interaction,anti-malarial	[30,31]
7	Eudistomin C	Eudistioma Sp.	Beta-carboline alkaloid	Cytotoic, anti-viral, inhibition of protein translation	[32]
8	Euseynstelamide B	Didemnum Candidum	Bis indole alkaloid	Cytotoxic,causing G2 arrest	[33]
9	Granulatimides	Didemnum granulatum	Alkaloid	Kinase inhibition	[34-36]
10	Irenecarbolines	Cnemidocarpa irene	Beta-carbolines	Enhancement of cholinergic neurotransmission	[37]
11	Lamellarins	Didemnum sp.	DOPA/TOPA derived pyrole alkaloids	Cytotoxic	[38-43]
12	Lissoclibadins	Lissoclinum of badium	Polysulfur aromatic alkaloids	Cytotoxic, antitumor in mice	[44]
13	Lissoclinamides	Lissoclinum patella	Cynobactins	Cytotoxic metal binding	[45]
14	Mandlalides A&B	Lissoclinum mandelai	Polyketides	Cytotoxic	[46-47]
15	Meridianins	Aplidium meridianum	Indole alkaloids	Kinase inhibition	[48-50]
16	Meridine	Amphicarpa meridian	Pyridoacridine Alkaloid	Cytotoxic	[51]
17	Ningalins	Didemnum sp.	DOPA/TOPA derived pyrrole alkaloids	MDR reversal, kinase inhibition	[52-54]
18	Patellamides	Lissoclinum patella	Cynobactins	Cytotoxic, metal binding	[55-57]
19	Patellazoles A-C	Lissoclinum patella	Polyketides	Cytotoxic, chemical defense	[58-60]
20	Phosphoeleganin	Sydnyum elegans	Polketide	Phosphatase inhibition	[61,62]
21	Pibocin, Varacin, Pictamine, Lepadin	.Eudistoma sp. Lissoclinum sp. Clavelina picta Clavelina lepadiformis	Ergoline alkaloid Benzopenththiepin Quinolizidine alkaloid Decahyrdoquionline alkaloid	Inhibition of cholinergic neurotransmission Inhibition of cholinergic neurotransmission	[63]
22	Polyandrocarpamines A& B	Polyandrocarpa sp.	2-aminoimidazolone alkaloid	Kinade inhibition	[64]
23	Pulmonarins A& B	Synoicum Pulmonaria	Dibrominated Tyrosine Derivatives	Enhancement of cholinergic Neurotransmission	[65]
24	Ritterazines	Riterella tokiada	Dimeric steroidal pyrazine alkaloids	Cytotoxic	[66-68]
25	Trabectidin(E T-473) Yondelis	Ectinascidia turbinata	Tetrahydroisoquinoline alkaloid	Anticancer drug(induces apoptosis in tumor associated macrophages)	[69-73]

3. CONCLUSION

In conclusion, bioactive compound derived from marine ascidians have a potential for human health care. The unique chemical classes of compounds found in the ascidians have promising biological activities which make them excellent candidates for drug design and development. The ascidians compounds are important for pharmaceutical studies and discovering new therapeutic treatment like anti-tumor/anticancer, anti-HIV, antimicrobial, and various diseases. In this review, we concluded Marine ascidians contains a wide range of secondary metabolites such as protein, peptides, alkaloids and minor metabolites might serve as vital role in future drug development.

4. FUTURE SCOPE

A further study on isolation, purification, structure determination and subsequent recognition of the novel mechanism of action of the clinically effective agent is suggested.

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