Review Article

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A review on marine immunomodulators

Vikrant Arya* and Vivek Kumar Gupta

Department of Pharmacognosy,

Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy,

Bela, Ropar, (Punjab) - India.

Abstract

Many natural products from marine sources are endowed with promising immunomodulating activities, thus representing invaluable leads in the drug discovery. The aim of this review is to highlight the work on natural immunomodulators from marine origin with around 35 naturally available marine sources have been explained. This review also discusses various chemical constituents responsible for immunomodulatory action along with their mechanism involved in immunomodulation. This work stimulates the researchers for further work on the marine immunomodulators.

Key-Words: Marine, Immunomodulatory, Immune system.

Introduction

Marine natural products

Natural products as crude materials with efficacy against various diseases have been selected by humans over many generations of practical experience. Such experiential evaluation is different from the scientific evaluation of western medicines and is underestimated sometimes. However many effective medicines, including as morphine, aspirin, atropine, ephedrine, reserpine and digitoxin were developed from natural products[1].

Natural products have always played an important role in medicine and in particular, marine metabolites have increasingly become major players in recent drug discovery. It depends on the structurally unique molecules produced by marine organisms, containing a significant number of stereogenic centres and halogen atoms, the latter introduced by metabolic processes of the inorganic species present in sea waters[2].

Recent studies of marine organisms have focused on their potential applications, particularly in the treatment of human diseases. Several marine natural products are currently in pre-clinical and clinical evaluation, others show promising biological activities[3].

*** Corresponding Author**

E mail: arya.vikrant30@gmail.com

Mob. 09736105832

New trends in drug discovery from natural sources emphasize on investigation of the marine ecosystem to explore numerous complex and novel chemical entities. These entities are the sources of new leads for treatment of many diseases such as cancer, AIDS, inflammatory conditions and a large variety of viral, bacterial and fungal diseases[4].

Marine chemicals have novel structures with pronounced biological activity and pharmacology. The study of such chemicals therefore is promising[5]. The potential for marine natural products as pharmaceutical was first developed in the 1950s which led to two marine derived pharmaceuticals that are still in use today. About 15,000 natural products have been described and about 30% of these natural products have been isolated from sponges Ara-C is an anti-cancer drug (used against non-Hodgkin's lymphoma and acute myelocytic leukemia) and Ara-A used as an antiviral drug for treating herpes[6].

Immunomodulators

These are biological or synthetic substances, which can stimulate, suppress or modulate any of the immune system including both adaptive and innate arms of the immune response. Clinically immunomodulators can be classified into following three categories.

Immunoadjuvants: These agents are used for enhancing vaccines efficacy and therefore, could be considered specific immune stimulants[7], example in this regard is of Freund's adjuvant[8]. The immunoadjuvants hold the promise of being the true modulators of immune response. It has proposed to

exploit them for selecting between cellular and humoral, Th1 (helper T1 cells) and Th2, (helper T2 cells) immunoprotective and immunodestructive, and reagenic (IgE) versus immunoglobin G (IgG) type of immune responses, which poses to be a real challenge to vaccine designers[7].

Immunostimulants: These agents are inherently non-specific in nature as they envisaged to enhance body's resistance against infection. They can act through innate immune response and through adaptive immune response. In healthy individuals the immunostimulants are expected to serve as prophylactic and promoter agents i.e. as immunopotentiators by enhancing basic level of immune response, and in the individual with impairment of immune response as immunotherapeutic agents[9].

Immunosuppressants: These are a structurally and functionally heterogeneous group of drugs, which are often concomitantly administered in combination regimens to treat various types of organ transplant rejection and autoimmune diseases[10]. Various marine sources used as immunomodulatory agents have been mentioned in table 1 given below.

Chemistry of marine immunomodulators[11-37]

Wide ranges of phytoconstituents as shown in figure 1. were responsible for immunomodulatory activity includes Cyclic depsipeptide, terpenes, polysaccharides (carbohydrates, uronic acids, sulphates), polyhydroxylated lactone, bioglycan, cyclic tripeptide, macrocyclic lactones *etc*. These marine constituents exert a desired pharmacological effect on body and thus act as natural immunomodulatory agents.

Conclusion

Marine have been a prime source of highly effective conventional drugs. Many studies have been performed to identify immunomodulator compounds with desired pharmacological activity and a limited toxicity. This review makes an attempt to give scientific account of use of valuable marine immunomodulatory sources. Some marine sources may stimulate the immune system like *Endarachne binghamiae, Gelliodes fibrosa, Sargassum ilicifolium, Phaeodactylum tricornutum etc* and some of them may suppress the immune responses example *Spirulina fusiformis, Chlorella stigmatophora, Tridemnum solidum, Euchelus asper etc.* Also the various secondary metabolites like Cyclic depsipeptide, terpenes, polysaccharides (carbohydrates, uronic acids, sulphates), polyhydroxylated lactone, bioglycan, cyclic tripeptide, macrocyclic lactones *etc*. have been exerting wide range of immunomodulating activity. Thus successful results have been achieved by following an appropriate screening approach.

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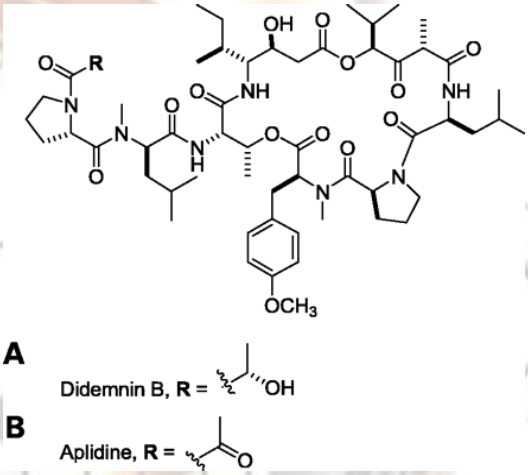

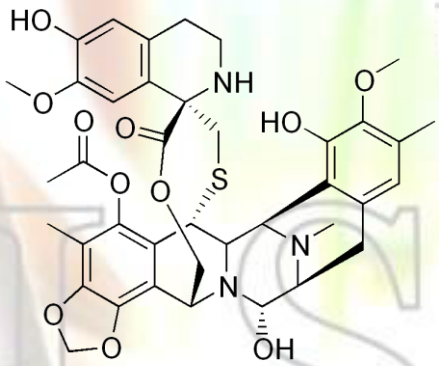

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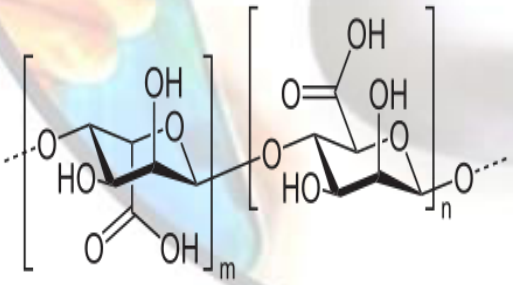
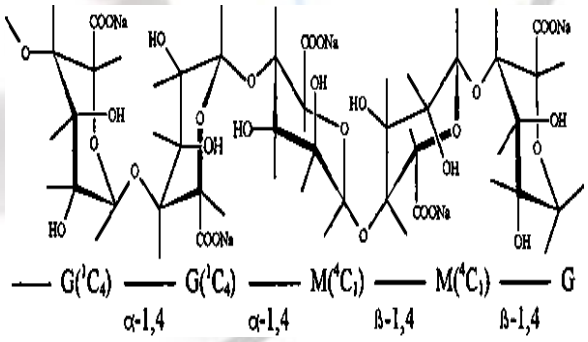


Alginic acid



Sodium alginate

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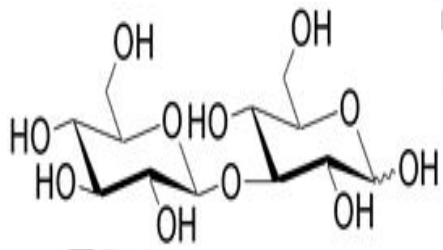
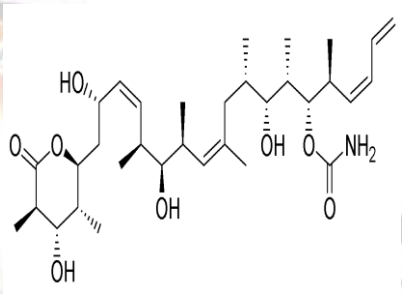
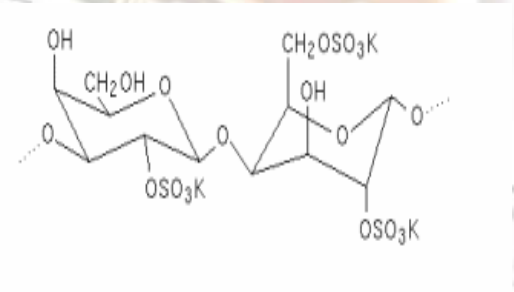
Laminarin

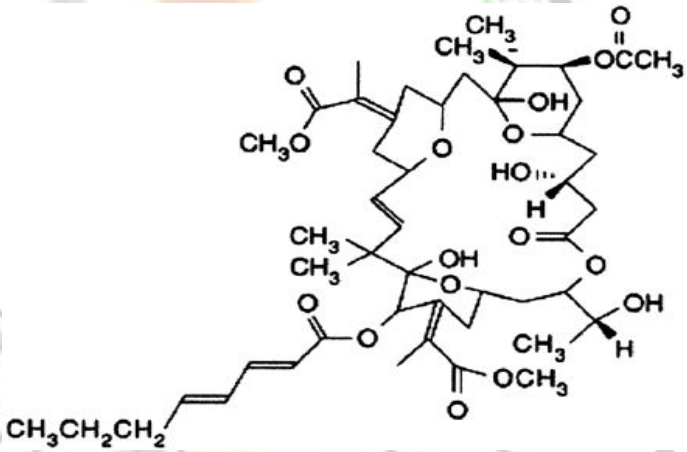


Discodermolide

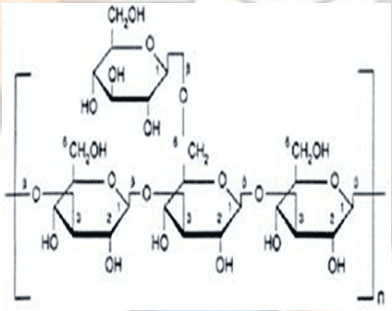




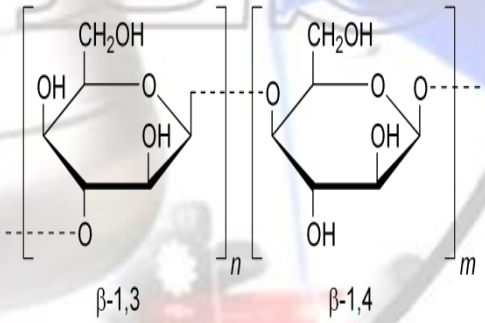
Carrageenan



Bryostatins



Polysaccharide



β-Glucan

Fig. 1: Chemical structures of reported marine immunomodulators

Table 1: Showing various marine immunomodulators[11-37]

Marine source	Chemical constituents	Immunomodulatory action
Aplidium albicans, Polyclinidae	Cyclic depsipeptide (Aplidin)	Aplidin caused *in vivo* anti-MM (multiple myeloma) activity in a xenograft plasmocytoma murine model
Hyrrios erecta, Thorectidae	Puupehedione, dipuupehedione, bispuupehenone	Puupehedione exerted a desired immunomodulatory potential
Curculigo orchioides, Hypoxidaceae	3,5-diacetoxy 2-methoxy 6-methyl phenyl acetic acid	Methanol extract seemed to work on both specific and non-specific immune pathways, whereas polysaccharide rich aqueous extract appeared to stimulate proinflammatory immune responses
Ecteinascidia turbinate, Perophoridae	Yondelis (Trabectedin)	Yondelis caused selective decrease of monocyte counts and of *ex vivo* macrophage differentiation
Endarachne binghamiae, Phaeophyceae	Polysaccharides (sodium alginate, alginic acid), glycoprotein	Sodium alginate exhibited strong stimulation activity for macrophage and T cell proliferation and also alginic acid but to a lesser extent. A glycoprotein isolated from the reported alga was also a strong proliferation stimulant. Additionally, it significantly induced the production of TNF-α and nitric oxide by macrophages and IFN-γ by T cells in a concentration-dependent manner. These assay results suggested that alginate and protein of the reported alga could be promising immune stimulants and modulants
Gelliodes fibrosa, Niphatidae	Terpenes, steroids and lipids	The ethyl acetate extracts of *G. fibrosa* on *in vivo* carbon clearance test have shown moderate immunostimulantory effect
Tedania anhelans, Tedaniidae	Terpenes, steroids and lipids	The ethyl acetate extracts of *T. anhelans* on *in vivo* carbon clearance test have shown moderate immunostimulantory effect *In vitro* study revealed that *T. anhelans* stimulated chemotatic, phagocytic and intracellular killing of human neutrophils
Sargassum ilicifolium, Sargassaceae	Terpenes, steroids and lipids	*S. ilicifolium* have shown prominient immunostimulatory effect. *In vitro* study revealed that *S.ilicifolium* stimulated chemotatic, phagocytic and intracellular killing of human neutrophils
Ircinia variabilis, Irciniidae	Fasciculatin(sesterterpenes)	Fasciculatin showed a moderate cytotoxicity and no selectivity on the cancer cell lines. Immunomodulatory activity of Fasciculatin found that it was inactive on human lymphocyte proliferation
Laminaria japonica, Laminariaceae	Laminarin oligosaccharides, polysaccharides	A mouse cDNA microarray showing the genes coding for immune response proteins were induced and apoptotic cell death proteins were reduced significantly by LO (Laminarin oligosaccharides) provided preliminary information regarding the immunomodulatory mechanism of LO

Lepeophtheirus salmonis, Caligidae	Trypsins	*L. salmonis* caused inhibitory effect on one centrally involved inflammatory gene (IL-1β)
Litopenaeus vannamei, Penaeoidea	Polysaccharides	Results indicated that the immunomodulatory action of superoxide dismutase (SOD) and its possible use as an indicator of immune responses
Nematopaleamon tenuipes, Penaeidae	Fractions of Petroleum ether: ethyl acetate (1:1) containing constituents	The Delayed type Hypersensitive reaction assay showed stimulation, whereas in the PFC(Plaque Forming Cell) assay it showed immunosuppression
Hemifusus pugilinus, Melongenidae	Fractions of Petroleum ether: ethyl acetate (1:1) containing constituents	The Delayed type Hypersensitive reaction assay showed stimulation. In the PFC assay it showed immunostimulation
Rastrelliger kanagurta, Scombridae	Fractions of Petroleum ether: ethyl acetate (1:1) containing constituents	Fractions showed stimulation in Delayed type Hypersensitive reaction assay. In the PFC assay it showed immunostimulation
Euchelus asper, Trochidae	Fractions of Petroleum ether: ethyl acetate (1:1) containing constituents	Fractions were less effective in the Delayed type Hypersensitive reaction assay showed stimulation. In the PFC assay it showed immunosuppression
Monostroma nitidum, Gomontiaceae	Sulfated polysaccharides (carbohydrates, uronic acids, sulphates)	Polysaccharides stimulated a macrophage cell line, Raw 264.7 cells, inducing considerable NO (nitric oxide) and PGE(2), production, which suggested that they could be strong immunomodulators
Dendrilla nigra, Dysideidae	Lipopolysaccharides	*Dendrilla* medicated group exhibited enhanced phagocytosis against *E. coli*
Ulva fasciata, Ulvaceae	Lipopolysaccharides	*Ulva* diet significantly increased the defense factors such as haemogram, agglutination index, phagocytic rate, bacterial clearance and serum bactericidal activity of treated shrimps over the control group
Theonella swinhoei, Theonellidae	Cyclic peptides, barangamides B, C, and D and a new depsipeptide, theonellapeptolide	Theonellapeptolides showed mild immunosuppressive activity
Hijikia fusiforme, Sargassaceae	Polysaccharide	Enhancing activity for the proliferative response of spleen cells in endotoxin-nonresponder C3H/HeJ mice
Gyrodinium impudicum, Picornaviridae	Polysaccharide	*G. impudicum* showed immunostimulatory effects and enhanced the tumoricidal activities of macrophages and NK cells *in vivo*
Sargassum thunbergii, Sargassaceae	Polysaccharide (Fucoidan)	Fucoidan enhanced the phagocytosis and chemiluminescence of macrophages
Meristotheca papulosa, Solieriaceae	Polysaccharide	Extracts of *M. papulosa* (green) markedly stimulated human lymphocytes to proliferate
Chondrus ocellatus, Gigartinaceae	Carrangeenans	In this study, tumor-inhibiting activities, weight of immune organ, nature killer cells activity, lymphocyte proliferation ratio and pathological slice of spleen and tumor cells from the control group and λ-carrageenan-treated mice of transplanted S180 and H22 tumor were investigated. The results indicated that the five λ-carrageenan samples showed antitumor and immunomodulation activities

Micrococcus luteus Micrococcaceae	Anti-*Micrococcus luteus* antibodies	Selective T cell immunosuppressive potential
Bugula neritina, Bugulidae	Macrocyclic lactones (Bryostatins)	Bryostatin 1 was found to bind to protein kinase C with high affinity, which may be the mechanistic basis for both observed anticancer and immunostimulating activities
Tridemnum solidum, Didemnidae	Depsipeptides (Didemnin B)	*T. solidum* extract showed immunosuppresive activities
Discodermia species, Theonellidae	Polyhydroxylated lactone (Discodermolide)	*Discodermia* showed immunosuppresive and cytotoxic activity
Lyngbya majuscule, Oscillatoriaceae	Peptides (Microcolin-A)	*L. majuscule* showed inhibitory effect against innate immune system (immunosuppressive)
Reniera species, Chalinidae	Cyclic Tripeptide (Renieramide)	*Reniera* showed immunomodulating activity in preliminary tests
Crenomytilus grayanus, Mytilidae	Bioglycan (Mytilan)	Mytilan isolated from the mantle of the mussel *C. grayanus* possessed high immunomodulating activity
Chlorella stigmatophora Syngnathidae	Polysaccharide	*C. stigmatophora* extract showed immunosuppressant effects
Phaeodactylum tricornutum, Phaeodactylaceae	Polysaccharide	*P. tricornutum* extract showed immunostimulatory effects
Chlorella pyrenoidosa, Mytilidae	Polysaccharide	Oral administration of *C. pyrenoidosa* polysaccharides, significantly enhanced phagocytic rate and phagocytic index
Spirulina fusiformis, Oscillatoriaceae	Polysaccharide	*S. fusiformis* showed immunosuppressive effect