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Review Article

Indian Marine Pharmacology: A Sneak Peek Into the Ecosystem

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This article tries to sift and collate the current status of the Marine Pharmacology with specific reference to the Indian contributions. The rich and diverse marine flora and fauna along the Indian coastline offers a wealth of resources to explore and exploit towards the benefit of the human health ranging from antioxidants/anti-inflammatory to antibacterials/ antimicrobials to anticancer entities and further to those that affect metabolic syndromes. It specifically outlines the range of chemical entities and/or their derivatives that are explored from the marine ecosystems towards various pharmacological indications.

Keywords: Marine Pharmacology; Marine Flora and Fauna; Ecosystems; Indian Research

Introduction

Marine biodiversity harbours variety of life in the sea, encompassing variation at levels of complexity from within species to across ecosystems. India is among one of the 12 mega biodiversity countries and 25 hot-spots possessing the highly enriched and highly endangered eco-regions of the world. India is the only country among Asian countries that has a long recorded inventory of coastal and marine biodiversity dating back to at least two centuries, having a coastline of about 7517 km, 5423 km along the mainland and 2094 km in the Andaman and Nicobar Islands and Lakshadweep Islands. It has in its realm around 844 species of seaweeds distributed among 217 genera, 486 species of sponges and 218 species of hard corals. Despite having such abundant resources only a select few marine organism are known for their usefulness in public domain (Mittermeier *et al*.,2000; Demunshi and Chug, 2009).

Oceans account for more than 80% of diverse plant and animal species in the world. Marine organisms such as sponges, tunicates, fishes, soft corals, nudibranchs, sea hares, opisthobranch molluscs, echinoderms, bryozoans, prawns, shells, sea slugs, and marine microorganisms are the main sources of bioactive materials (viz., oils and cosmetics) (Donia and Hamann 2003).

Indian coastline spreading for over 8000km is interspersed with varied clusters of marine habitats like inter-tidal rocky, muddy and sandy shores, coral reefs, and mangrove forests. In spite of having such abundant resources at its disposal the potential of Indian marine resources seems untapped in terms of new drug discovery or biotechnological advancement undertakings. Institutes such as National Institute of Oceanology, Goa; Central Drug Research Institute, Lucknow; Bose Institute, Kolkata; Central Institute of Fisheries Education, Mumbai; Regional Research Laboratory, Bhubaneswar of Council for Scientific and Industrial Research are currently involved in drug development programmes from marine sources. Various research institutes, academia and pharmaceutical industry are recognising and collaborating to tap the potential of our marine resources (Thakur *et al*., 2005).

Considering the abundance and potential for large scale production there is a need to review marine pharmacology for the development of new drug moiety. At present, the pharmaceutical industry is working towards phytochemical screening and isolation of novel molecules with unreported pharmacological properties that can be exploited for

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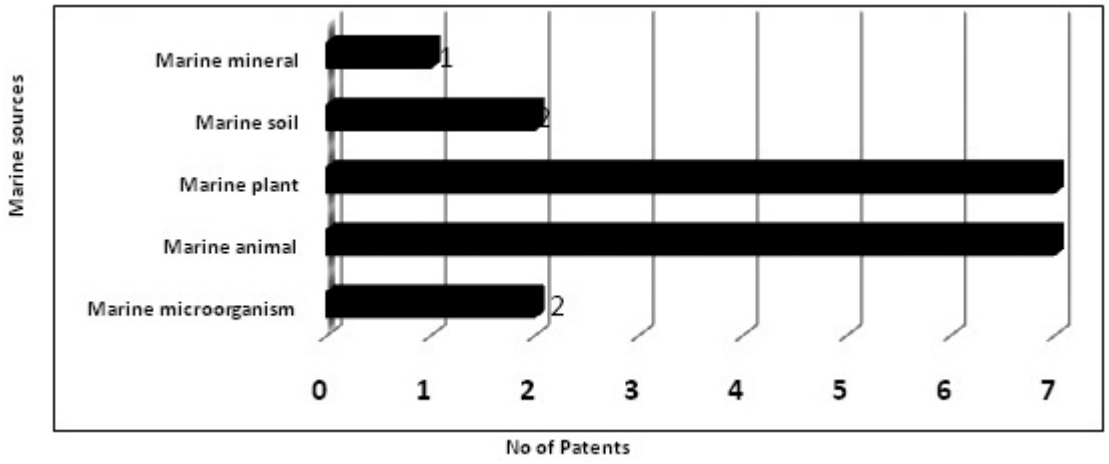
the development of new therapeutic agents and further commercialization. This review has largely focused on different classes of marine drugs currently in use and at different stages of trials for approval and marketing in future. The review has also tried to delve into the challenges and future strategies for drug development from marine sources (Malve, 2016).

On the basis of assignee analysis of the marine based patents in India CSIR has emerged as the leader in terms of patents filed in marine biodiversity (Table 1). Patent analysis also indicates a gradual rise in the number of patents filed relating to marine biodiversity. This indicates a paradigm shift of the scientific community to exploit the vast untapped resources of the ocean flora and fauna (Table 2). The major marine sources identified according to patent data and scientific publications are mangrove, marine actinomycetes and sediment, fish, marine bacteria, marine plants, marine sponge and marine algae (Table 3).

Marine pharmacology can be classified on the basis of source of the candidate drug (Murti and Agarwal, 2010)

- Genetically engineered marine organisms
- Manufacture of pharmaceuticals and nutraceuticals of marine origin
- Chemicals produced by or found in marine organisms shown to have a wide variety of applications as pharmaceuticals (Table 4).

Patent trends in India have indicated that main focus of research has been extraction i.e. highest number of patents has been filed for method of extraction, followed by isolation. Only one formulation based patent from marine source has been reported, indicating this area of research virtually untapped. The scientific publication analysis also gives a similar result whereby main focus is on extraction and isolation (Table 5).



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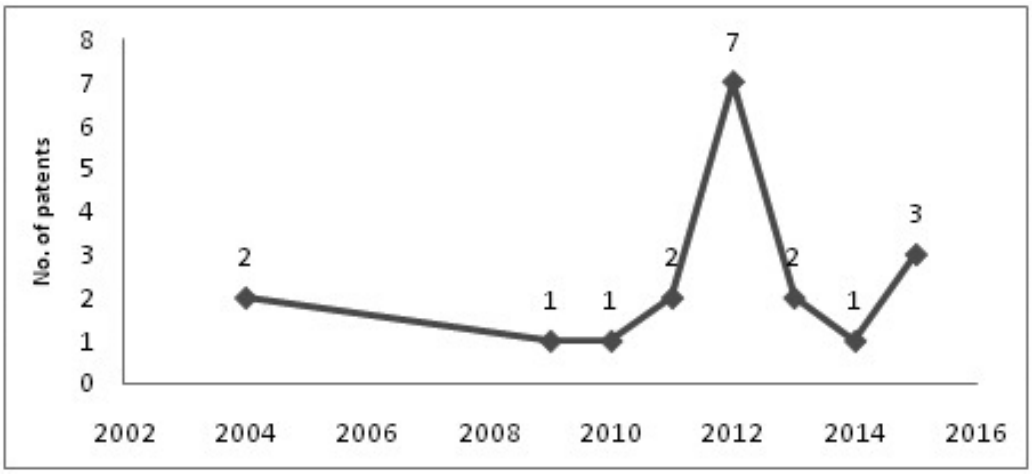

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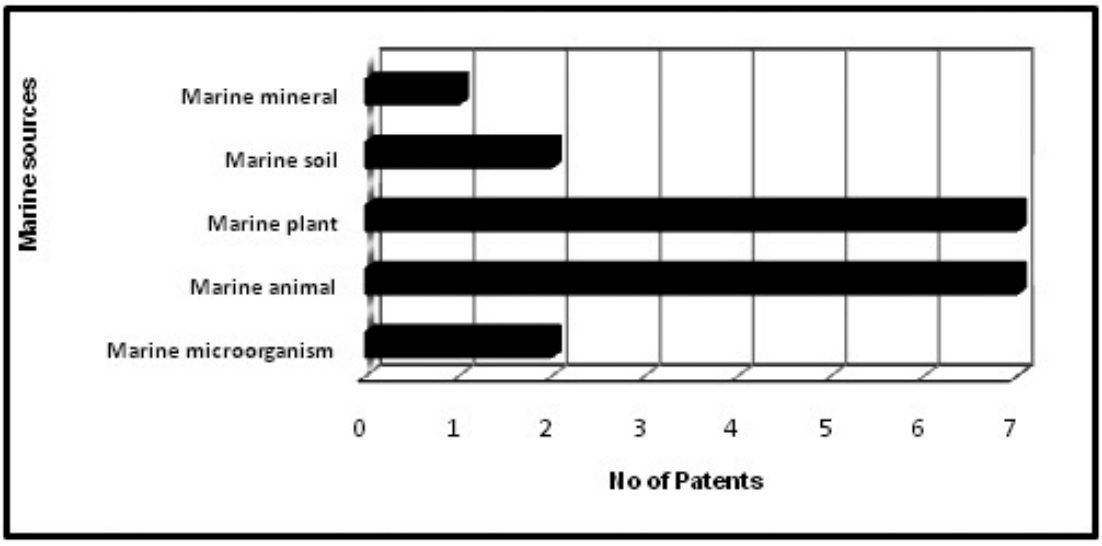

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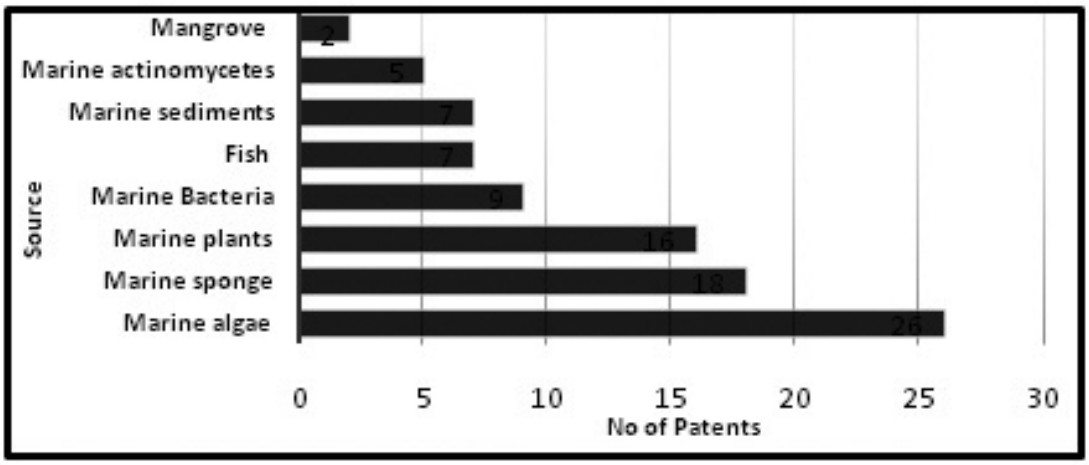

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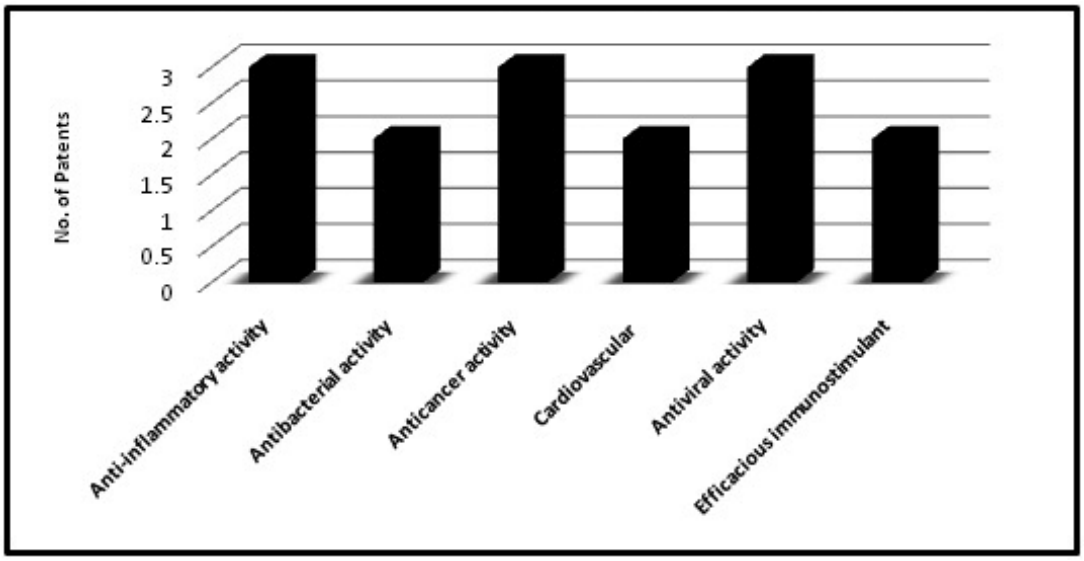

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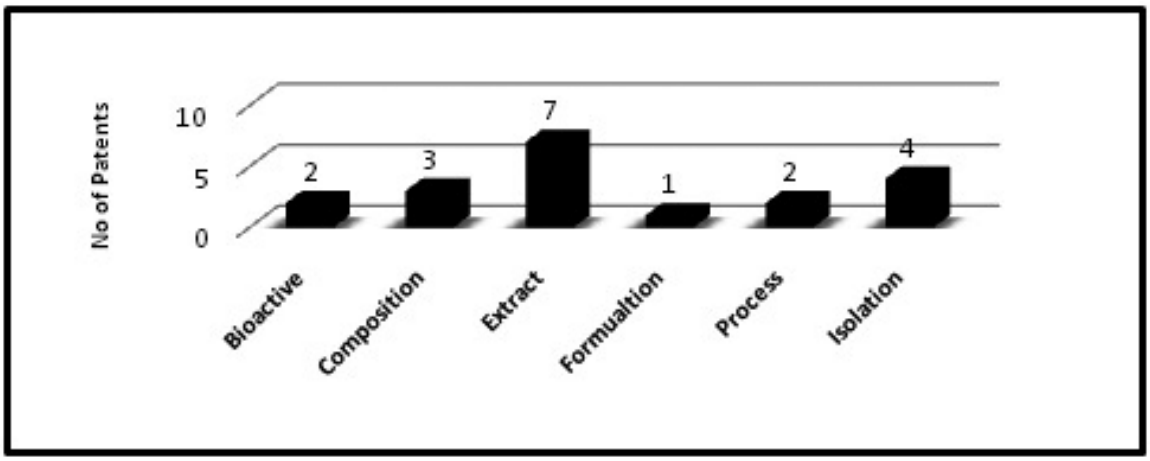

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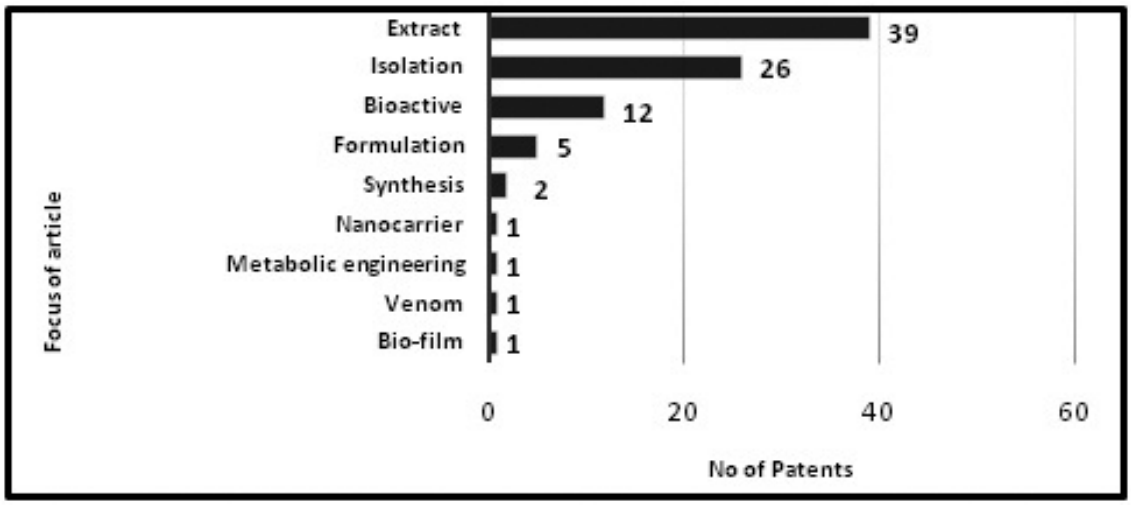


Table 5B:

Marine drugs can be broadly classified based on their actions as follows:

Anti-Inflammatory/Antioxidant

Two new chromenyl derivatives, characterized as 7-(2'-ethyl-1'-hydroxynonan-2'-yl)-6,7,8,8a-tetrahydro-3H-isochromen-1-(5H)-one (Fig. 1) and 6(1)-(3-((E)-3(1b)-(furan-2'-yl)-prop-3(1b)-en-3(1)-yl)-4a,5,6,8a-tetrahydro-8-methyl-2H-chromen-6-yl)-ethyl-5''-methyl-hexanoate (Fig. 2) isolated from ethyl acetate-methanol extract of yellow-foot bivalve clam, *Paphia malabarica* exhibited considerable radical scavenging activities with alpha-tocopherol. The anti-5-lipoxygenase activity of the two compounds was significantly more than ibuprofen indicating their potential as anti-inflammatory compounds (Joy and Chakraborty, 2017).

Marineactinomycetes identified as *Streptomyces sparsus* upon analysis revealed the presence of

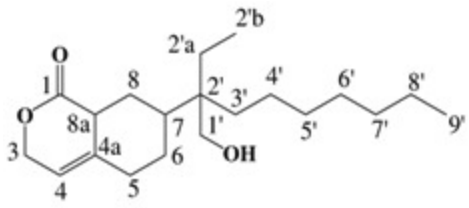


Fig. 1:

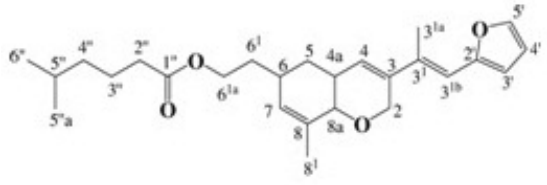


Fig. 2:

tryptophan dehydrobutyrine-diketo-piperazine, maculosin, 7-o-demethyl albocycline, albocycline M-2, and 7-o-demethoxy-7-oxo albocycline in a negative ion mode. the spectroscopical analysis showed various compounds like dotriacontane, tetracosane 11-decyl-, diheptyl phthalate, 1-hexadecanesulfonyl chloride, L-alanyl-L-tryptophan, phthalic acid ethyl pentyl ester, 4-trifluoroacetoxyhexadecane, and 1H-imidazole 4,5-dihydro-2,4 dimethyl. Indicating that ethyl acetate extract of *Streptomyces sparsus* VSM-30 may have antibacterial, antifungal, and antioxidant activities (Managamuri *et al*., 2017).

Two novel sterols (22E)-24(1), 24(2)-methyldihomocholest-5, 22-dien-3-ol and 23-gem-dimethylcholesta-5-en-3-ol obtained from the south-west coast of Arabian Sea ,showing anti-inflammatory potential against cyclooxygenase-2 and 5-lipoxygenase were isolated from *Paphia malabarica*. The derivative (22E)-24(1), 24(2)-methyldihomocholest-5, 22-dien-3-ol, showed antioxidant and anti-inflammatory activity significantly greater than 23-gem-dimethylcholesta-5-en-3-ol (Joy *et al*., 2017).

The Bacterial strain *Vibrio* Spp. (PIGB 184) isolated from Arabian Sea composed of phenol, 2,4-bis(1,1-dimethylethyl) and pyrrolo[1,2-a]pyrazine-1,4-dione,hexahydro-3-(2-methylpropyl) showed the production of pigmentary antioxidants (Pawar *et al*., 2016).

The evaluation of three marine diatoms, *Chaetoceros curvisetus, Thalassiosira subtilis* and *Odontella aurita* for antioxidant activity, DPPH radical scavenging activity, nitric oxide radical scavenging activity, hydrogen peroxide radical scavenging activity and ferric reducing power indicated that the methanolic extract of *O. aurita* had the maximum total phenolic content and antioxidant property. Total phenol content, total antioxidant activity, DPPH radical scavenging activity (15.25%), hydrogen peroxide radical scavenging activity (54.73%), Ferric reducing power assay and nitric oxide radical scavenging activity were highest in *C. curvisetus* (32.37%) (Hemalata *et al*., 2015).

The pigmented bacteria associated with seaweed possess large number of antioxidant compounds and need to be extracted in large scale for clinical studies and use. A Sargassum associated yellowish brown pigmented bacteria *Pseudomonas koreensis* (JX915782) showed more activity when compared to standard antioxidant butylated hydroxytoluene (BHT) against DPPH scavenging. Similarly *Serratia rubidaea* (JX915783), an associate of *Ulva* Spp. and *Pseudomonas argentinensis* (JX915781) an epiphyte of *Chaetomorpha* media, also showed antioxidant activity. It was concluded by gene sequencing analysis bacteria that have higher antioxidant activity belongs to the class *Gammaproteobacteria* (Pawar *et al*., 2015).

Two marine red algae *Gelidiella acerosa* and *Sargassum wightii* showed excellent antioxidant and anticholinesterase activity. The comet assay analysing the genotoxic activity showed that PBMC (peripheral blood mononuclear cells) treated with seaweed extracts exhibited less or no damage to cells, thus proving the non-genotoxic nature of the extract (Syad and Kasi, 2014).

Alginic acid isolated from the brown algae *Sargassum wightii* in type II collagen induced arthritic studies in rat showed Treatment with alginic acid significantly reduced the activities of inflammatory marker enzymes like cycloxygenase-2 (COX-2), lipoxygenase (5-LOX), xanthine oxidase (XO) and myeloperoxidase (MPO) rheumatoid factor (RF), ceruloplasmin and C-reactive protein (CRP). Concentrations of proinflammatory cytokines like IL-1 beta, TNF alpha and IL-6 were lowered on treatment with alginic acid. It also reduced the activities of lysosomal enzymes that manifest the systemic damage during arthritis. Treatment with alginic acid indicated that it reduced extensive bone degradation and synovial hyperplasia associated with arthritis, suggesting that aliginic acid can be used for the treatment of rheumatoid arthritis (Saritha Kumari and Kurup, 2013).

Kappaphycus alvarezii (Doty) a marine alga belonging to order: *Gigartinales* and family: *Solieriaceae* grows in southeast coast of India. The antioxidant and antigenotoxic/protective studies indicated that long-term administration of *K. alvarezii* extract had antioxidant potential and provided protection against tissue lipid peroxidation and cell damage, making it useful in the food and pharmaceutical industries (Nagarani and Kumaraguru, 2012).

Sargassum myriocystum a sulphated

polysaccharide identified as Fucoidan showed potential radical scavenging activity compared to butylated hydroxyl toluene, Fig. 3 (Badrinathan *et al*., 2012). Mi-64, a high molecular weight protein (130 kDa), obtained from marine polychaete (*Mastobranchus indicus*) collected from the Indian Sunderban significantly inhibited the overproduction of interleukin-1 beta, interleukin-6, chemoattractant-1, and tumor necrosis factor-alpha and augmented interleukin -10 production. The study indicated the role of Mi-64 as potential antiarthritic agent (Alam *et al.*, 2012).

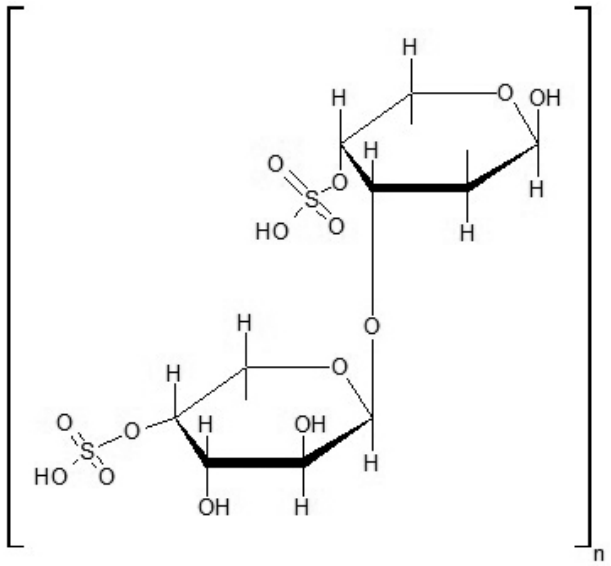


Fig. 3:

Antibacterial/Antimicrobial

Marine cyanobacterium *Oscillatoriaa cuminata* NTAPC05 methanol extract was fractionated and a new monogalactosyl diacyl glycerol having palmitoyl (MGDG-palmitoyl), was obtained showing bactericidal property against beta lactamase ESBL-producing bacteria (Ahamed *et al*., 2017).

The study on marine actinomycetes was found to contain biologically active compounds that control plant diseases. Many extracts showed strong antifungal and antibacterial activity against *Erwinia caratovora, Pyriculariae oryzae, Aspergillus niger* and *Trichoderma* (Dhevagi *et al*., 2017).

The identification of four species of solitary ascidians and four colonial ascidians from Thoothukudi coast showed that extract of extracellular products (ECP) had weak inhibitory activity against test organisms, but the ethyl acetate crude extract of both cell and cell free supernatants exhibited strong inhibitory activity. *Eudistoma viride* methanolic extract also showed good antagonistic activity against *Vibrio cholerae* and *V. harveyi* (Mary *et al.*, 2016).

The diatom *Amphora* cf. *capitellata* from Aegean Sea was studies for its antimicrobial activity against *Candida albicans* the ethanolic extract showed considerable activity while the extract of diatom *Nitzschia communis* showed effective results against Gram-positive bacterium, *S. aureus*. *Laurencia papillosa a red algae and* three *Cystoseira* species extracts showed selective anti-proliferative activity against cancer cell lines whereas *Dilophus fasciola a* brown alga showed the highest anti-inflammatory activity as measured in primary microglial and astrocyte cell cultures and also by reduction of pro-inflammatory cytokines (Montalvao *et al*., 2016).

Bacillus subtilis sub spp. *spizizenii* and *B. thuringiensis* isolated from hydrothermal vent region of Azorean Island Faial, North Atlantic Ocean exhibited antagonistic activity in their cell free extracts against *Vibrio cholera* serogroup 01 and *Staphylococcus aureus*, respectively. Both bacterial strains showed sensitivity to protease test indicating the proteinaceous nature of the antibacterial substances. Zebra fish animal model was used instead of antibiotic test to evaluate the toxicity studies including heat resistance, proteinaceous nature and bacteriostatic mode of action. The *Staphylococcus aureus*-zebra fish embryo infection studies indicated that Bacillus showed no toxic effects (Ravindran *et al*., 2016).

Kahalalide F (KF) along with two unprecedented related peptides were isolated from ethanolic-methanolic extracts of *Elysiaornata* mucus demonstrating antifungal activity. The kahalalides Z exhibited significant antimicrobial properties against various fungal pathogens which infected many economically important plants, food and fish.The Kahalalides were also found to inhibit the *in-vitro* growth of a series of cancer cell lines comparable to that of with KF (Ciavatta *et al*., 2016).

Ethyl acetate and chloroform extracts of *Penicillium chrysogenum* strain isolated from *Tedaniaanhelans* (marine sponge) from Indian Ocean

exhibited antibacterial activity with later showing more activity. The chloroform extract showed activity against *Mycobacterium tuberculosis* H37Ra, *Mycobacterium avium, Mycobacterium fortuitum, Mycobacterium smegmatis, Mycobacterium vaccae, Staphylococcus aureus, Aeromonas hydrophila, Pseudomonas aeruginosa* and *Vibrio cholerae*. The extract did not show cytotoxic ctivity in vero cell lines. Antibacterial activity might be due to diketopiperazines, Cyclo-(L-Pro-L-Phe) and Cyclo-(L-Leu-L-Pro) produced by the associated fungi-*P. chrysogenum* (Visamsetti *et al*., 2016).

Stylissamide G a natural heptacyclopeptide, previously isolated from the Bahamian marine sponge *Stylissacaribica* from the Caribbean Sea, was synthesized by coupling of the tetrapeptide l-phenylalanyl-l-prolyl-l-phenylalanyl-l-proline methyl ester with the tripeptide Boc-l-leucyl-l-isoleucyl-l-proline, followed by cyclization of the linear heptapeptide fragment (Fig. 4). It displayed good anti-helminthic potential against *Megascoplex konkanensis, Pontoscotex core thruses* and *Eudrilus eugeniea,* and potent antifungal activity against pathogenic *Candida albicans* and dermatophytes *Trichophyton mentagrophytes* and *Microsporum audouinii* (Dahiya *et al*., 2016).

Fungistatic activity against pathogenic *Candida albicans* was exhibited by peptide Cm-p5 (SRSE-LIVHQRLF derived from the marine mollusc *Cenchritis muricatus*. The peptide also exhibited low toxic effects against a cultured mammalian cell line. Cm-p5 possessed alpha-helical structure a characterized by circular dichroism and nuclear magnetic resonance revealed an alpha-helical structure and a tendency to random coil folding in aqueous solutions. Cm-p5 also has a high affinity for the phospholipids of fungal membranes (phosphatidylserine and phosphatidylethanolamine), and lesser affinity to mammalian membrane phospholipid. It also showed low interaction with ergosterol and no interaction with chitin (Lopez *et al.*, 2015).

Caulerpa racemosa, a marine alga was used to synthesize Silver nanoparticles which exhibited good antibacterial activity against human pathogens such as *Staphylococcus aureus* and *Proteus mirabilis* (Kathiraven *et al*., 2015).

Pond sediments of Ribandar saltern, Goa were studied in three media viz. Starch casein, R2A and Inorganic salt starch agar at various salinities. Halotolerant and halophilic Actinomycetales producing anti-bacterial metabolites were identified. Most of them were halotolerant *Streptomyces* Spp. others being rare actinomycetes viz. *Nocardiopsis, Micromonospora* and *Kocuria* spp. More than 50% of the isolates showed anti-bacterial activity against one or more of the fifteen human pathogens tested. Eight strains from 4 genera were studied in detail and showed consistent anti-bacterial activity. Multiple inhibitions against test organisms were shown by four *Streptomyces* strains while four rare actinomycetes were specific in their inhibitory activity. Halophilic *Kocuria* spp., *Nocardiopsis* spp., and halotolerant *Micromonospora* spp. produced anti-bacterial compound(s) against *Staphylococcus aureus, Staphylococcus citreus,* and *Vibrio cholerae*, respectively. This indicated that halophilic and halotolerant actinomycetes from marine salterns are a potential source of anti-bacterial compounds (Ballav *et al.*, 2015).

Dual behaviour of the marine antimicrobial peptides (AMP), tachyplesin was studied. This cyclic peptide is known to possess antimicrobial properties. It was further investigated for its cell-penetrating property and cargo delivery ability. It showed higher stability *in vitro* due to its marine nature and cyclic structure. Its role as cell-penetrating peptide is well known. Since it delivers cargo molecules in both living systems, it is an efficient nonviral macromolecule nanocarrier (Jain *et al*., 2015).

A marine bacterium with mosquitocidal effect was isolated from the gut region of the marine red snapper fish (*Lutjanus sanguineous*). The isolated bacterium belonged to the strain *Bacillus cereus* VCRC-B540. Biochemical studies showed that the strain could be useful in mosquito control. It exhibited toxicity against *Culex quinquefasciatus, Anopheles stephensi* and *Aedes aegyptii*, without negative effects for the non-targeted organisms *Chironomus riparius, Daphnia cephalata* and *Notonecta glauca*. A polypeptide (M.wt: 90 kDa) identified as a surface layer protein was instrumental for the toxicity observed (Mani *et al*., 2015).

The larvicidal potential of the Taiwanese seaweed *Gracilaria firma* and extracts combined with the copepod *Megacyclops formosanus* were studied for controlling dengue vector *Aedes aegyptii*. Methanolic extract of *G. firma* showed significant larvicidal activity against *A. aegypti* larvae. This could provide an eco-friendly approach to eradicating larvae of the dengue vector *A. aegyptii* (Kalimuthu *et al*., 2014).

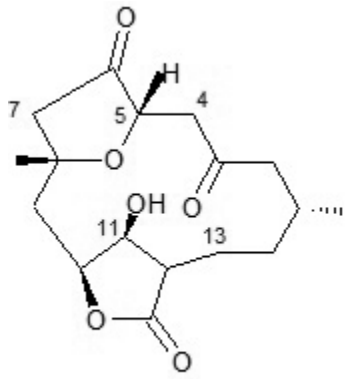
Secondary metabolites isolated from eighty four different fungal endophytes from sea grasses (5), marine algae (36) and leaves or barks of forest trees (43) grown *in vitro* were harvested by immobilizing them on XAD beads. They exhibited antiplasmodial activity against blood stage *Plasmodium falciparum* in human red blood cell culture using SYBR Green I assay.The studies indicated that fungal endophytes can be an untapped resource for secondary metabolites showing various bioactivities including anti malarials (Kaushik *et al*., 2014).

A bacterium isolated from marine soil of strain, *Enterobacter cloacae* VCRC-B519 showed toxicity for *Culex quinquefasciatus, Anopheles stephensi* and *Aedes aegyptii,* in increasing order without negative effects for non-targeted organisms *Chironomus riparius, Daphnia cephalata* and *Notonecta glauca*. *E. cloacae* analyses indicated the toxicity exhibited was due to three polypeptides (M.wt: 25, 30 and 50 kDa). The polypeptides were found to be enzymatic in nature and their peptide sequences were identified to be polysugar degrading enzymes (25 kDa), cell wall associated hydrolases (30 kDa) and amino peptidase (50 kDa) (Poopathi *et al*., 2014).

Marine *Streptomyces* spp. VITJS4 crude extracts were studied for their larvicidal and repellent activities. The ethyl acetate crude showed 100% mortality for all the 3 species after 24 h exposure against the early fourth instar larvae of malarial vector *Anopheles stephensi*, dengue vector –*Aedes aegyptii* and filariasis vector –*Culex quinquefasciatus*. The ethyl acetate extract also showed complete protection against these mosquito bites (Naine and Devi, 2014).

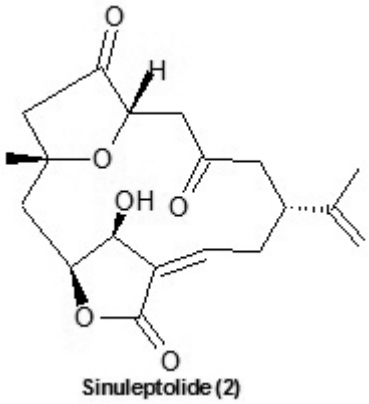
Mosquitocidal bacterium isolated from marine soil from east coastal areas of Pondicherry (India) belonged to *Bacillus cereus* VCRC-B520 .Toxicity assay indicated that the bacterium isolate was more effective against filariasis vector, *Culex quinquefasciatus,* than the other two species (*Anopheles stephensi* and *Aedesa egyptii*). The protein identified was an endotoxin-specific insecticidal, namely "Cry4Aa"(85 kDa) for mosquitocidal action, thus providing an environmental friendly alternative to synthetic pesticides (Poopathi *et al.,* 2014)

Six known norcembranoids(1-6) and one new compound, named kavaranolide extracted from the Indian soft coral, *Sinularia kavarattiensis* showed promising activity against the Chikungunya virus (CHIKV) replicon. Compounds 1-3 and 5-7 (Fig. 5) isolated from crude extract and exhibited replicon-inhibiting potential in the CHIKV model by using a luminescence-based detection technique and live cell imaging. Compounds 1 and 2 along with CHIKV replicon inhibition also showed cytotoxic properties. Compound 2 showed anti-inflammatory activity due to release of pro- and anti-inflammatory cytokines (Lillsunde *et al.,* 2014).



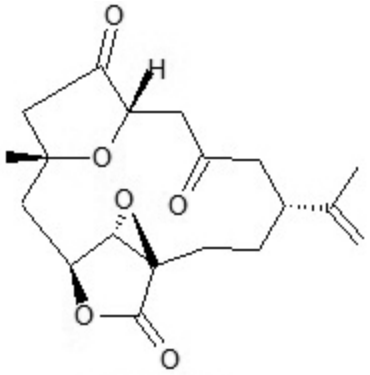
5-epi-sinuleptolide (1)

Fig. 5A:



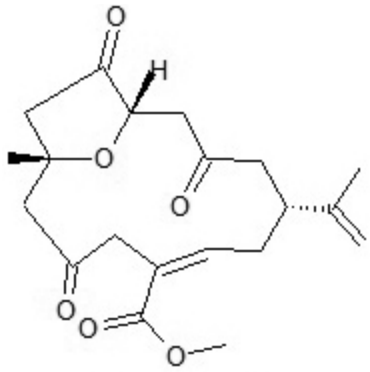
Sinuleptolide (2)

Fig. 5B:



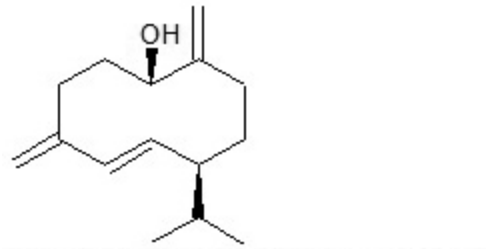
Scabrolide D(3)

Fig. 5C:



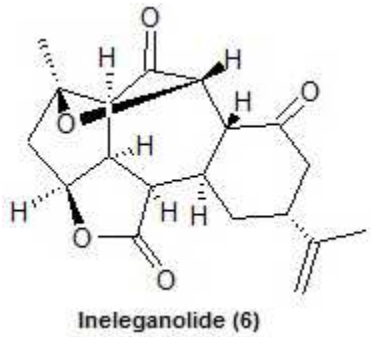
Norcembranoid (4)

Fig. 5D:



ent-germacra-4(15),5E,10(14)-triene-1β-ol (5)

Fig. 5E:



Ineleganolide (6)

Fig. 5E:

Isatin and its synthetic analogues were evaluated for their antibacterial. Few synthetically modified isatin exhibited potent inhibitory activity against *Planococcus donghaensis, Erythrobacter litoralis, Aliivibrio salmonicida* and *Vibrio furnisii*. The study showed that the modified analogues showed better anti-inflammatory activity than their parent marine compound isatin.The modified analogue 1H-indole-2, 3-dione can be used as antifouling anti-inflammatory agent (Fig. 6) (Majik *et al*., 2014).

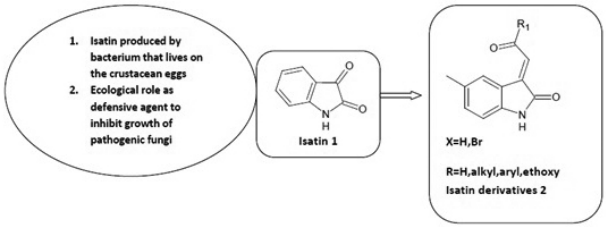


Fig. 6:

Twenty-nine actinobacterial strains isolated from marine sponge *Spongia officinalis* and showed antagonistic activity against various bacterial and fungal pathogens. The strain that produced the active antibiotic MAPS15 was identified as *Streptomyces* spp. active fraction was purified and characterized and assumed to be a pyrrolidone derivative which showed bioactivity against different pathogens suggesting that this strain can be utilized to produce antibiotics. (Sathiyanarayanan *et al.*, 2014).

Bacterial biosymbionts associated with marine sponges from Gulf of Mannar, South Coast India exhibited antimicrobial potential of the flurophoric and chromophoric metabolites extracted. The metabolites extracted showed high therapeutic potential against many bacterial pathogens including multidrug-resistant strains. The secondary metabolites were characterized and were found to be quinones, alkaloids, flavanoids and flavonyl glycosides. Ethyl acetate extracts of chromophore and floureophore substances showed significant inhibitory properties against Methicillin resistant *Staphylococcus aureus* (MRSA) and *Salmonella typhi* respectively. The chomophore-producing strain were closely related to Pseudomonas spp. RHLB12, isolated from *Callyspongia* spp. and floureophore-producing bacteria was related to *Bacillus licheniformis* T6-1 which was isolated from *Haliclona* spp. (Skariyachan *et al.*, 2014).

Methanol extract of thirty-eight seaweeds samples were screened against *Laurencia papillosa* (*Ceramiales, Rhodomelaceae, Rhodophyta*) exhibited highest antimicrobial activity among the thirty eight seaweed samples screened against Gram-positive (*Staphylococcus aureus* ATCC 25923 and *Bacillus subtilis* ATCC 6051) and gram negative (*Escherichia coli* ATCC 8739 and *Pseudomonas aerugenosa* ATCC 9027) bacteria. It also exhibited antibacterial activity against four clinical Gram-negative isolates (*E. coli, P. aerugenosa, Klebsiella pneumoniae* and *Shigella flexineri*).The active fraction was identified as a cholesterol derivative, 24-propylidene cholest-5-en-3 beta-ol (Fig. 7) (Kavita *et al.*, 2014).

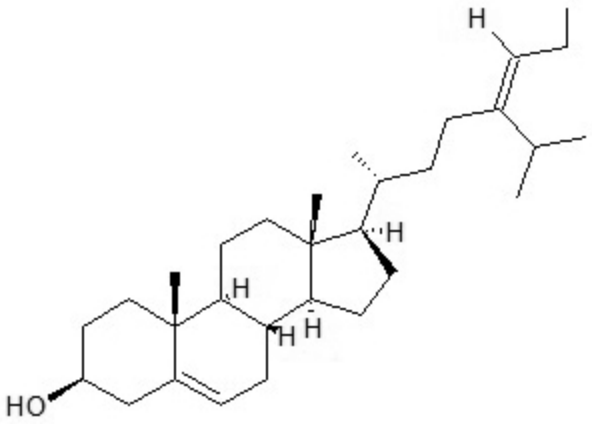


Fig. 7:

A group of 168 marine bacteria isolated from different marine organisms from Pulicat lake, coromandal coast in south India, were tested against five test strains, viz., *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus* and *Candida albicans*. Of these the two bacterial strains, *S. aureus* and *K. pneumoniae* showed broad spectrum antibacterial activities (Chellaram and Praveen, 2014).

In-vivo screening of *Alcaligenes faecalis* from *Caenorhabditis elegans* showed that it inhibits the virulence of *Vibrio alginolyticus* by interrupting the QS pathway. The study showed that *C. elegans* based *in-vivo* screening method can be used to identify bioactives (Durai *et al.*, 2013).

Organic extracts of seaweeds (*Ulva fasciata* and *Hypnea musciformis)*, sponges (*Dendrilla nigra, Axinella donnai* and *Clathria gorgonoides*) and a holothurian (*Holothuria scabra*) were used for the detection of microalgal lethality potential. Antifouling activity of *H. Scabra* may be due to its toxic secondary metabolites. Although all extracts inhibited the growth of microalgae at various concentrations except *H. musciformis* and *A. donnani*, which showed reverse effect by inducing the growth of microalgae to certain extent. Suggesting that 'microalgal lethality bioassay' can be used for the detection of biotoxic and antifouling agents from marine organisms (Manilal *et al.*, 2013).

Bacillus licheniformis strain D1 isolated from the surface of green mussel, *Perna viridis* showed antimicrobial activity against pathogenic *Candida albicans* BH, *Pseudomonas aeruginosa* PAO1 *Bacillus pumilus* TiO1 cultures. On analysis antimicrobial agent was found to be a 14 kDa protein designated as BL-DZ1. The protein inhibited microbial growth, decreased biofilm formation and dispersed pre-formed biofilms of the representative cultures in polystyrene microtiter plates and on glass surfaces (Dusane *et al.*, 2013).

Bacillus licheniformis, collected off the coast of Cochin, India, inhibited the growth of Gram-positive test organisms. Bacteriocin BL8 was found to be pH-tolerant and thermostable and active against the tested Gram-positive bacteria, was isolated from *Bacillus licheniformis*. This bacteriocin can be an effective therapeutic agent and can be used as biopreservative in food processing industry (Smitha and Bhat, 2013).

The acaricidal and insecticidal property of ethyl acetate extract and its compounds isolated from marine actinobacteria, *Streptomyces* VITSTK7 sp were evaluated against the larvae of cattle ticks, *Haemaphysalis bispinosa* and *Rhipicephalus (Boophilus) microplus* (Acari: Ixodidae); fourth-instar larvae of malaria vector, *Anopheles* subpictus; and filarial vector, *Culex quinquefasciatus*. The identified compounds were cyclopentanepropanoic acid, 3,5-bis(acetyloxy)-2-[3-(methoxyimino)octyl], methyl ester (structure1, Fig. 8); 5-azidomethyl-3-(2-ethoxy carbonyl-ethyl)-4-ethoxycarbonylmethyl-1H-pyrrole-2-carboxylic acid, ethyl ester (structure 2, Fig. 8); and akuammilan-16-carboxylic acid, 17-(acetyloxy)-10-methoxy, methyl ester (16R) (structure 3, Fig. 8). The maximum efficacy was observed in compounds 1, 2, and 3, and the ethyl acetate extract

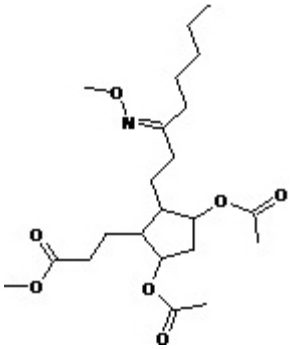


Fig. 8A:

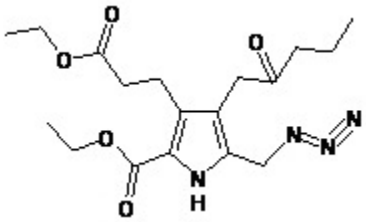


Fig. 8B:

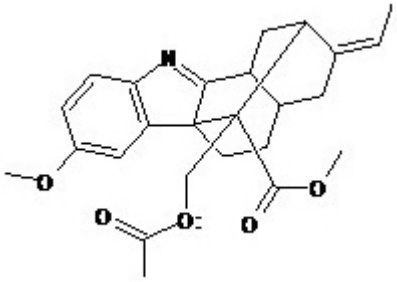


Fig. 8C:

of *Streptomyces* VITSTK7 sp. against the larvae of *H. bispinosa*, *R. microplus*, *A. subpictus* and *C. Quinque fasciatus* (Fig. 8) (Thenmozhi *et al.*, 2013).

An indole and a diketopiperazine moiety were isolated from the culture medium of *Penicillium chrysogenum*, (MTCC 5108), an endophytic fungus on the mangrove plant *Porteresia coarctata* (Roxb.). The cell free culture medium of *P. chrysogenum* showed effective activity against *Vibrio cholerae*, (MCM B-322), a pathogen causing cholera in humans. On chemical analysis compound of formula $C_{19}H_{21}O_2N_3$was isolated. Its antibacterial activity was comparable with standard antibiotic, streptomycin. This was found to be (3,1'-didehydro-3[2aEuro(3)(3'aEuro(3),3'aEuro(3)-dimethyl-prop-2-enyl)-3aEuro(3)-indolylmethylene]-6-methyl piperazine-2,5-dione) (Fig. 9) (Devi *et al.*, 2012).

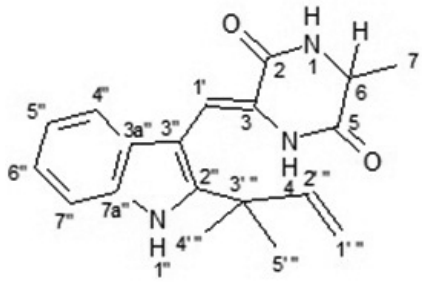


Fig. 9:

Bio-silver nanoparticles were synthesised from Marine algae *Padina pavonica* (Linn.) thallus broth. The thallus extract as well as silver-based nanoparticles of marine alga, *P. Pavonica* (Linn.) were tested against two important pathogens of cotton. *Fusarium* wilts (*Fusarium oxysporumf.* Spp. *vasinfectum*) and bacterial leaf blight (*Xanthomonas campestris* pv. *malvacearum*). The *P. pavonica* based silver nanoparticles inhibited the growth of the test pathogens and can be used for the management of cotton phytopathogens (Sahayaraj *et al*., 2012).

A 100 heterotrophic, halophilic bacterial bionts isolated from 9 sponges, 5 corals and one bivalve were evaluated for their antibacterial activity. Culture broths of 46 of these bionts were active against human pathogenic bacteria namely *Staphylococcus citreus, Proteus vulgaris, Serratio marcesans, Salmonella typhi, Aerobacter aerogenes* and *Escherichia coli*. Larger number of bionts was isolated from corals followed by sponges and bivalve. Making them rich source of bioactive secondary metabolites against human bacterial pathogens (Velho and Furtado, 2012).

Ascidian *Lissoclinum fragile*, found in the coastal waters of Tuticorin Southeast coast of India were investigated for their bioactive potential. In antibacterial assay bacterial pathogen, *S. typhi* exhibit high zone of inhibition against dichloromethane extract. In antifungal assay, fungal pathogen *Penicillium* species showed high zone of inhibition against n-butanol extract. In haemolytic assay, n-butanol extract showed high heamolytic activity in chicken erythrocytes, goat erythrocytes and cow erythrocytes. In cytotoxic activity, n-butanol extract exhibited high LC_{50} value against brine shrimps indicating that the ascidian *L. fragile* has remarkable antimicrobial, haemolytic, and cytotoxic activities (Kumaran *et al*., 2012).

Four species of seaweeds collected from the Kollam coast (Indian Ocean) were used to isolate 27 epiphytic bacteria and investigated for antagonistic activity by cross streak method. Of the 27 bacterial isolates, 4 strains inhibited the growth of at least one shrimp *Vibrio* pathogen tested. The SWI-24 strain exhibited highest spectrum of activity against all the tested shrimp pathogens. The active isolate of SWI-24 was found to be *Pseudoalteromonas* spp. and further reflect the potential use of seaweed-associated bacteria in managing the shrimp/fish disease (Sugathan *et al.*, 2012).

Twenty five marine soil samples were collected from the region of Palk Strait of Bay of Bengal, Tamil Nadu, and were subjected to the isolation of actinomycetes. Sixty-eight morphologically distinct isolates were obtained and 37% *i.e.* twenty five of them had antimicrobial activity. The phylogenetic evaluation categorized the organism as *Streptomyces afghaniensis* VPTS3-1 (Vijayakumar *et al*., 2017).

The leaf extracts of *Rhizophora mucronata* L., were screened for antibacterial activity against multi-drug resistant *Vibrio harveyi* and *Vibrio campbellii* isolated from Lobster's larvae hatchery water. *V. harveyi* was found highly resistant to ampicillin, oxacillin, cephalothin, vancomycin, erythromycin, and clidamycin, but sensitive towards chloramphenicol and gentamycin. Whereas, *Vibrio campbellii* was found highly resistant to ampicillin, oxacillin, cephalothin, vancomycin, and erythromycin, *Vibrio campbellii* was highly sensitive to chloramphenicol and moderately sensitive to clindamycin, and gentamycin. Chloroform leaf extract of *Rhizophora mucronata* L. Showed highest activity against both *Vibrio* spp., while, hexane, ethyl acetate, and methanol extract revealed moderate activity against both *Vibrio* spp. (Baskaran and Mohan, 2012).

Thirty-three bacterial isolates were isolated from *Haliclona grant*, and the extracellular ethyl acetate extracts were screened for antiplasmodial activity against *Plasmodium falciparum*. The antiplasmodial activity of bacterium RJAUTHB 14 is highly comparable with the positive control chloroquine.The antiplasmodial activity may be due to the presence of reducing sugars and alkaloids in the ethyl acetate extracts of bacterium RJAUTHB 14 (Inbaneson and Ravikumar, 2012).

The antioxidant and antimicrobial activities of *Chaetomorpha linum* from the Mandapam coastal region of the Gulf of Mannar, on the southeast coast of India, were examined based on the free radical-scavenging activity of the 1, 1-diphenyl-2-picrylhydrazyl radical (DPPH), ferrous reducing antioxidant property (FRAP), and total phenolic content in the methanolic extract. Indicating that *C. linum* has potential as a natural antioxidant and a natural source of antimicrobials against many microbes (Senthilkumar and Sudha, 2012).

Chloroform extract of *Rhizophora mucronata*, collected from Pitchavaram, Muthupett and Manakudy regions of Tamilnadu, were chromatographed for identification of triterpenoids such as betulin and lupeol proving their antimalarial and antiviral activities (Hridya *et al*., 2012).

Fasciospongia cavernosa doc var. brown (dark brown) and *Fasciospongia cavernosa* doc var.yellow (yellow) were collected from the Vishakhapatnam coast of Bay of Bengal and investigated for their antimicrobial activity. 178 microorganisms isolated from different parts of the two sponges mostly from the middle part of the sponge and showed antimicrobial activities against Gram-positive (*Staphylococcus aureus, Bacillus subtilis, Bacillus cereus*) Gram-negative bacteria (*Pseudomonas aeruginosa, Escherichia coli, Proteus vulgaris*), fungi (*Candida albicans, Aspergillus niger*) and 10 other pathogenic organisms (Kumar *et al.*, 2012).

Themethanolic and crude extract of brown alga, *Lobophora variegata* showed toxicity in all organisms including pathogenic bacteria, mosquito pupae, nematodes and plant seeds in the given order i.e. highest for pathogenic bacteria and least for plant seeds. The fatty acids present in the fraction of *L. variegata* extract may be responsible for the said activity (Manilal *et al.*, 2012).

Anti Cancer/Cytotoxic Activity

A 131 isolates belonging to the phylum: *Gammaproteobacteria* (63%), *Bacillales* (34%) and *Micrococcaceae* (3%) were isolated from surficial sediments of south east Arabian Sea and evaluated. Among these, about 40% of the isolates showed the presence of secondary metabolite biosynthetic genes such as PKS or NRPS or both. Nearly 50% were

cytotoxic to human breast cancer MCF-7 cells and were bactericidal to human pathogens, *Escherichia coli* and *Pseudomonas* spp., while 20-30% of them were bactericidal to *Vibrio* spp. and *Staphylococcus* spp. In all, 8 isolates, belonging to *Pseudomonas* spp., *Bacillus* spp. and/or *Lysinibacillus* spp. displayed high level of bactericidal and cytotoxic properties (Anas *et al.*, 2016).

Marine stingray *Dasyatis sephen* produced venom which was found to enhance lipid peroxidative markers such as thiobarbituric acid reactive substance, conjugated diene, and lipid hydroperoxide in HeLa cell lines. Stingray venom apart from increasing ROS levels also altered the mitochondrial membrane potential in HeLa cells. Apoptotic morphological alterations in *D. sephen* venom-treated groups were also increased (Rajesh Kumar*et al.*, 2015).

Anticancer activity of ethanolic extract of *Sargassum wightii* Greville a marine brown alga belonging to the *Sargassaceae* family was investigated in mice using DAL cell lines to induce cancer. Cancer cell counts in mice were significantly increased on intraperitoneal inoculation of DAL cells. This increase in cancer cell count upon administration of ethanolic extract of *S. wightii* indicates that the brown alga has a significant inhibitory effect on the tumor cell proliferation. Administration of ethanolic extract also showed a significant decrease in tumor weight, restored the hematological parameters in DAL-treated mice and hence increased the lifespan of DAL-treated mice (Anjana *et al.*, 2014).

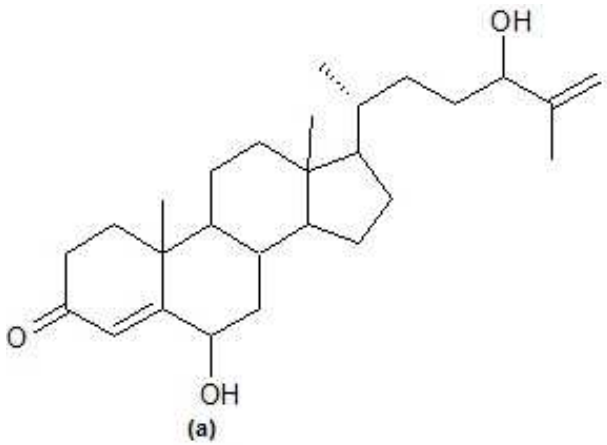
Antitumor potential of ethanolic extract of *Gracilaria edulis* J. Ag (Brown algae) was evaluated against the Ehrlich ascites tumour *in-vivo* and *in-vitro*. *In-vitro* cytotoxic studies indicated that ethanol extract of *Gracilaria edulis* showed cytotoxicity to *Ehrlich ascites* tumour cells due to its ability to produce reactive oxygen species and therefore decreasing intracellular glutathione responsible for the apoptotic activity of the extract (Patra and Muthuraman, 2013).

The antiangiogenic and antiproliferative activity of *Chlorella pyrenoidosa* was evaluated in experimental models of angiogenesis and by cell proliferation assay (MTT). The secondary metabolites of *C. pyrenoidosa* extract indicated significant antiangiogenic activity against vascular endothelial growth factor induced neovascularization and antiproliferation activity of the assay (Kyadari *et al.*, 2013).

The anti-metastatic potential of the methanolic extract of *Rhizophora apiculata (R. apiculata)* was evaluated using the B16F-10 melanoma induced lung metastasis model in mice. Administration of the methanolic extract inhibited the pulmonary tumor nodule formation as well as increased the life span (survival rate) of the metastatic tumour bearing mice. It also reduced biochemical parameters such as lung collagen hydroxyproline, hexosamine, uronic acid content, serum nitric oxide (NO), gamma-glutamyltranspeptidase (GGT) and sialic acid levels when compared to metastasis controls (Prabhu and Guruvayoorappan, 2013).

Four lead compounds (RL381, RL366, RL376 and RG012) were analysed for their ability to bind at taxol binding site. They showed better interactions with the H1-S2 loop and M-loop which are actively involved in lateral interactions of tubulins and also with the helix H7 which is the connecting link between N-terminal and intermediate domain. The residues obtained by these lead compounds on polar interaction were D224, H227, R276, R282 and R359 which closely mimicked the interaction of taxol with beta-tubulin (Fig. 10) (Kumar *et al.*, 2013).

The anti-inflammatory and anti-tumour activity ofmethanolic extract of *Rhizophora apiculata* was



(a)

Fig. 10A:

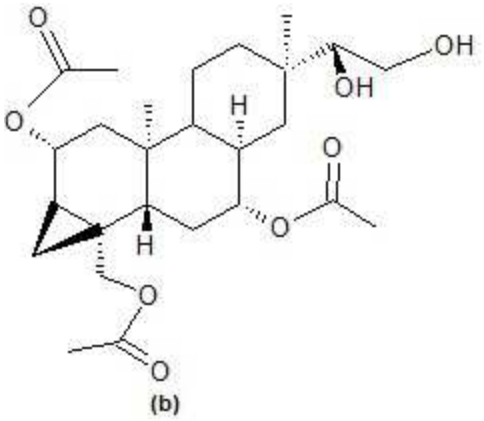


Fig. 10B:

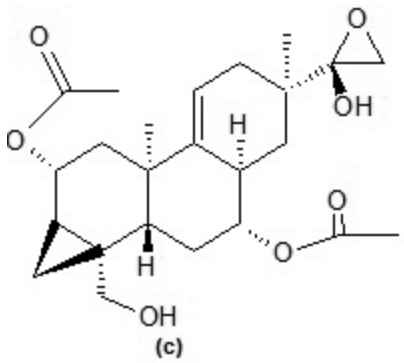


Fig. 10C:

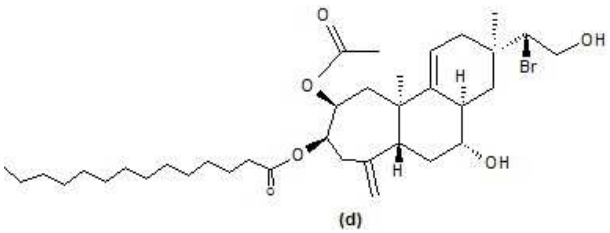


Fig. 10D:

evaluated against B16F10 melanoma cells in mice. *R. apiculata* extract was shown to inhibit the solid tumour development, significantly reduced tumor cell glutathione (GSH) levels, serum gamma-glutamyltranspeptidase (GGT) and nitric oxide (NO) levels in the tumor-induced mice. The extract also reduces total white blood cell count and hemoglobin levels in tumour bearing mice. It also reduced acute inflammation (assessed as paw edema) induced by carrageenan and inflammation edema induced by formalin. Themethanolic extract was found to possess active constituents like 4-pyrrolidinyl, pyrazole, and ketone derivatives (Prabhu and Guruvayoorappan, 2012).

Immunostimulant/Immunomodulatory

Common carp *Cyprinus carpio* which fed on marine alga, *Padinagymno spora* rich in polysaccharides was found to have active immune system. Diet rich in polysaccharide protected the fish from its common pathogens like *Aeromonas hydrophila* and *Edwardsiella tarda* with relative percent survival (RPS) values of 80 and 60 respectively. The immune parameters like serum lysozyme, myeloperoxidase activities and antibody response were also improved in the fish which took algal diet. Immunostimulation by *P. gymnospora* might be due to the increased secretion of cytokine interleukin-1 beta (IL-1 beta) and antimicrobial peptide lysozyme-C (Rajendran *et al.*, 2016).

Seven Monoindole derivatives isolated from the MeOH extract of marine sponge *Spongosorite shalichondriodes* from western coast of India (Fig. 11). The investigation of immunomodulatory activities of methanolic extract were studied for acute toxicity. Parameters studied for Immunomodulatory potential were Haemagglutinating antibody (HA), delayed-type hypersensitivity (DTH) response and cyclophosphamide-induced myelosuppression. Marine sponge *Spongosorite shalichondrioides* was found

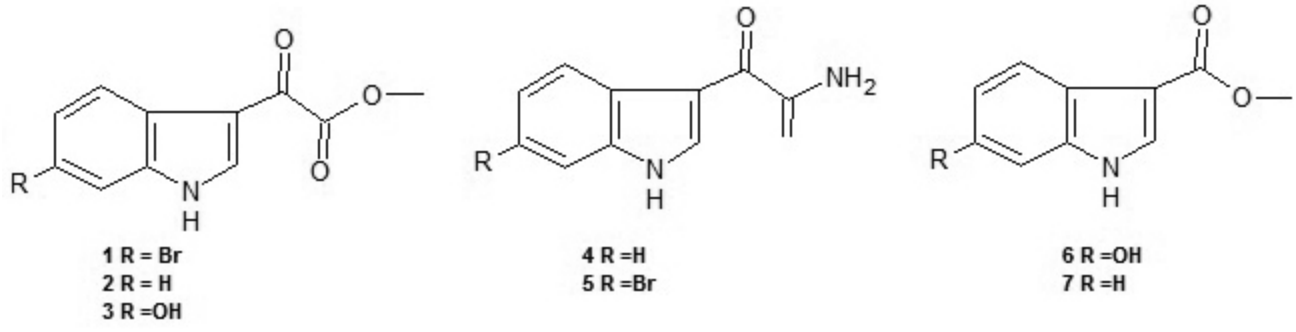


Fig. 11:

to have immunosuppressant activity and may possess compounds which can be used for organ rejection treatment (Kumar MS *et al.*, 2012).

Wound Dressing

A collagen films (CF) was prepared using the bones of *Bluefin trevally* (BT) which showed potential as a wound dressing material. CF showed biocompatibility to human keratinocyte cell line (HaCaT) and better mechanical properties in in-vitro studies. The CF film treated mice also showed faster wound healing properties demonstrating that fish waste can be used for the preparation of a value-added product like wound dressing material (Rethinam *et al.*, 2016).

Fish scales a biological waste product in marine food industry was used to prepare collagen sponge. Collagen sponge incorporated separately with drug mupirocin and *Macrotylomau niflorum* plant extract. The incorporated collagen sponge enhanced wound healing and was involved in the increase of growth factors such as vascular endothelial growth factor, fibroblast growth factor, epidermal growth factor and transforming growth factor beta. Increased levels of hydroxyproline, hexosamine and uronic acid were observed in the *Macrotyloma uniflorum* plant extract treated group compared with the other groups. The *Macrotyloma uniflorum* plant extract collagen sponge reduced inflammation and accelerated matrix metalloproteinases and scar formation, thereby contributing to faster wound healing (Muthukumar *et al.*, 2014).

Wound healing activity of Type I collagen extracted from the bone of two marine fishes; *Magalaspiscordyla* and *Otolithesruber* were studied. The cross-linked structure of collagen with glutaraldehyde with three dimensional pores improved the wound healing property of the bandage (Kumar *et al.*, 2012).

Antidiabetic

Evaluation of four green algae *Chaetomorpha aerea, Enteromorpha intestinalis, Chlorodesmis* Spp., and *Cladophora rupestris* for *in-vitro* alpha-amylase, alpha-glucosidase inhibitory, and antioxidant activity showed that chloroform extract of *C. aerea* and methanol extract of *Chlorodesmis* showed effective inhibition against alpha-amylase. Methanol extract of *C. rupestris* indicated free radical scavenging activity. Phenol, 2, 4-bis (1, 1-dimethylethyl) and z, z-6,28-heptatriactontadien-2-one were major constituents in the methanol extract of *C. rupestris* and chloroform extract of *C. Aerea* (Fig. 12) (Unnikrishnan *et al.*, 2015).

A significant number of marine bacteria under wide range of bacterial phyla such as *Firmicutes* (23), *Actinobacteria* (9), *Proteobacteria* (7) and *Bacteroidetes* (1), were found to produce beta-glucosidase inhibitors for use as anti-diabetics, anti-

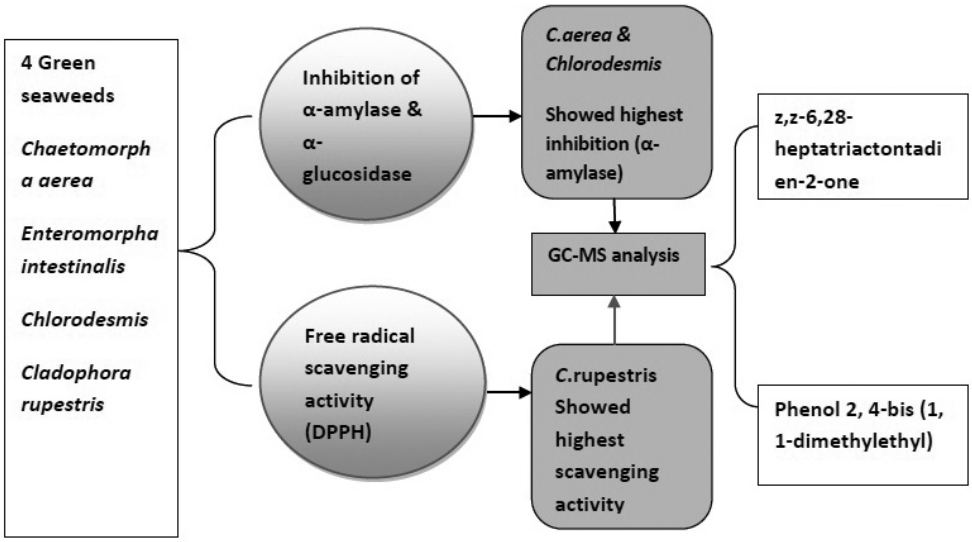


Fig. 12:

obesity and anti-tumour compounds (Pandey *et al.*, 2013).

Miscellaneous

The screening of 887 marine bacteria for acetylcholinesterase inhibitors showed that 140 of them inhibit the electric eel enzyme, acetylcholinesterase in a microplate based assay. Larger amount of acetylcholinesterase inhibitors were bacterial associates of soft corals followed by sediment isolates while most of the potent inhibitors belonged to the bacterial associates of marine sponges. The strain M18SP4P showed maximum inhibition (54%) and was isolated from the marine sponge *Fasciospongia cavernosa*. The strain was identified as *Bacillus subtilis* (Pandey *et al.*, 2014).

The herbicidal activity of the crude extracts and partially purified fractions of *Trochus tentorium* was assayed using the duckweed, *Lemna minor* L. by benchtop bioassay. The crude acetone extract of *T tentorium* decayed the fronds of *Lemna* plants on the 4th day, while ethyl acetate, dichloromethane and methanol extracts showed decay of the plants on the 5th day of the experiment. The study indicated that column purified acetone fractions of the gastropod was able to decay *L. minor* to a better degree in comparison with the crude extracts. (Chellaram *et al.*, 2012).

The anti-genotoxic potential of crude aqueous extracts of *Kappaphycus alvarezii* (Rhodophyceae), collected from the Southeast coast of India was evaluated. Aqueous extract of *K. Alverazii* was found to interfere with the clastogenicity induced by mercury chloride ($HgCl_2$) in marine fish, *Therapon jarbua* by measuring cytogenetic endpoints like cell viability and comet assay. The result indicated the use of *K alvarezii* extract as fish supplement to reduce mercury poisoning in them as well avoiding human consumption of infected fish (Nagarani *et al.*, 2012).

Gold nanoparticles (AuNPs) were produced using marine bacteria *Marinobacter pelagius*. Stable, monodisperse AuNP with 10 nm dimension approximately were obtained by exposure of HAuCl4 solution to whole cells of a bacterial strain (Sharma *et al.*, 2012).

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