REVIEW OF LITERATURE

Natural products are the secondary or non primary metabolites produced by living organisms. Natural products have been exploited by people for a variety of purposes such as food, fragrances, pigments, insecticides and medicines. Historically plants have served as the major source of medicinally useful natural products developed from a legacy of folk medicine based on herbal remedies. Around 25% pharmaceutical drugs derived from plant natural products and an additional 12% are based on microbially produced natural products (Joffe and Thomas, 1989). The microbes, plant and invertebrate diversity in the marine environment may exceed that of terrestrial habitats and research on the use of marine natural products as pharmacological agents is only now becoming a mature discipline. The marine environment lacks an ethnomedical history and it is difficult to collect marine organisms (Faulkner, 1992).

Definitions of ‘Marine Biotechnology’ often refer to the vast potential of the oceans to lead to new cures for human and animal disease natural drugs has always been the most basic form of biotechnology. Though only initiated in the late 1970s’ natural drug discovery from the world’s oceans has been accelerated by the chemical uniqueness of marine organisms and be the need to develop drug for contemporary, difficult to cure, diseases. Current research activities primarily within the academic laboratories have generated convincing evidence that marine drug discovery has an exceedingly bright future (Fenical, 1997). By the early 1960s researchers began to view the oceans as a new and untouched source of potentially useful compounds perhaps not surprising considering that more than 90% of the Earth’s biosphere is ocean (Davidson, 1995).
The marine environment is an exceptional reservoir of bioactive natural products, many of which exhibit structural features not found in terrestrial natural products (Ireland et al., 1988). The chemists of marine natural products have determined the chemical structures of over 6000 new compounds (Munro et al., 1994). In 1996, Carte was reported biomedical potential of marine natural products and he revealed that marine organisms are yielding novel molecules for use in basic research and medical applications. Approximately 2500 new metabolites were reported from a variety of marine organisms during the decade from 1977 to 1987 (Ireland et al., 1993). Faulkner (1999) described the highlights of marine natural products chemistry (1972-1999). Moore’s (1999) review covers the literature published on the biosynthesis of marine microbial and macro algal natural products over 10 year period from 1989 through 1998. An earlier report by Garson surveyed the whole field of marine natural product biosynthesis through mid 1988 (Garson, 1989).

Bakus (1987) had reported that the coral reefs and assemblage of marine organisms which are potential source of a wide range of bioactive substances and also he had pointed out three major areas for marine natural product’s role such as 1) Antipredatory compounds 2) Antifouling compounds and 3) Competition for space. Several authors like Webber (1994); Gorbach (2001); Rhodes (2000) and Schmidt (2000) have reviewed the antibiotic resistance of the pathogens in aquaculture systems. Hence the need of the hour is to search for novel antibacterial compounds with therapeutic potential for which the pathogens may not have resistance (Patil et al., 2001). Many marine organisms such as bacteria (Abraham, 2004; Anderson et al., 1974; Chellaram et al., 2005 a. Maeda and Liao, 1992), sponges (Monks et al., 2002), seaweeds (Lemos et al., 1985; Moreau et al., 1984; Padmakumar and Ayyakannu, 1997;
Ravikumar et al., 2002; Vanitha et al., 2003; and Suressh Kumar et al., 2002), molluscs (Chellaram et al., 2004; Anand and Edward, 2002 and Gnanambal et al., 2005), molluscan egg masses (Benkendorff et al., 2001) and fishes (Ramkumar et al., 2005; Hellio et al., 2002 and Austin and Intosh, 1988) are already screened for their potential to inhibit the fish bacterial pathogens. It is believed that in general, phenolic compounds are widely distributed in marine plants and a number of biological functions have been attributed to them as indicated by Zapata and McMillan (1979); Harborne and Williams (1976); McMillan et al. (1980) and Glombitza and Knöss (1992). An earlier study of Harrison (1982) on leaf extracts suggests that phenolic constituents of seagrass may inhibit amphipod grazing and microbial growth.

Chemical studies of marine bacteria developing a new resource was reviewed by Fenical, (1993) and reported that the marine microorganisms have developed unique metabolic and physiological capabilities that not only ensure survival in extreme habitats but also offer the potential for the production of metabolites which would not be observed from terrestrial microorganisms. Halvorson (1998) had assessed that the marine organisms have evolved biochemical and physiological mechanisms that include the protection against predation, infection and competition. Proksch et al. (2002) had reported recently, that molecular methods have successfully been applied to study the microbial diversity in marine sponges. The strategies used for isolating and structural elucidation of pharmacologically active metabolites from marine organisms are discussed with examples of cytotoxic and antihistaminic compounds from marine echinoderms, sponges, gorgonians, ascidians and tunicates (Riguera, 1997). Narkowicz (2002); Kokke (1983); Gudbjarnason, (1999); Kijjoa and Sawangwong (2004) and Lei
and Zhou (2002) who discovered the marine natural products from marine invertebrates.

There are a copious number of authors like Maeda and Liao (1992); Maeda (1994); Douillet and Langdon (1994) and Dopazo et al. (1988) worked in developing antibiotics for the use in aquaculture. Antibacterials are applied to prevent diseases in shrimp hatcheries and salmon aquaculture farms throughout the world (GESAMP, 1997). Redshaw, (1995) and Bangkok Post (2000) have reported the potential effects of antibacterials used in aquaculture, aquatic environment and human health. Ma, et al. (2005) reported the effect of antibacterials use in aquaculture on biogeochemical processes in marine sediment.

It is proved that the imperative marine bioactive compounds are discovered from molluscs, soft corals, stony corals and Gorgonians by Coval and Scheuer (1982); Goh et al. (1995); Karuso and Scheuer (2002); Maruta et al. (2005); Maoka et al. (2005); Brecknell et al. (2000); Anjaneyulu et al. (2000); Zhang et al. (2003); Muralidhar et al. (2005); Watanabe et al. (2003); Radhika et al. (2004); Blunt et al. (2005); Kamel et al. (2004) and Xue et al. (2004); Lin et al. (2005); Yu-Chi-Lin et al. (2005); Sung et al. (2004); Ya-Ching-Shen et al. (2002); Blunt et al. (2005); Sung et al. (2004); Fung and Ding (1997) and Di Salvo (1971). Ascidians (Mendiola et al., 2007). Sponges (Tasdmir et al., 2001; Proksch, 1994; Patil et al., 2002; Goud et al., 2003; Jeong et al., 2003; Iwashima et al., 2002; Ravinder et al., 2005; Matsunaga et al., 2000; Patil et al., 2002; Agarwal and Bowden 2005; Rifai et al., 2004; Fattorusso et al., 2002; Hao et al., 2001; Santalova et al., 2004; Belarbi et al., 2003; Ely et al., 2004; Zhang et al., 2003; Giannini et al., 1999; Xue et al., 2004; Rifai et al., 2005; Weiss et al., 1995; Becerro et al., 1994;
Selvin et al., 2004 and Betancourt-Lozano et al. 1998; Giannini et al., 1999) and seaweeds (Kang et al. (2003) and Rahman et al. (2001) respectively.

Microorganisms particularly bacteria has a profound effect on the development of chemistry and medical science. The first antibiotic from a marine bacterium was described in 1966 (Burkholder et al.), the numbers of new compounds are increased constantly during the later years. Few compounds from marine organisms might be interesting for the pharmaceutical market (Faulkner, 2000). Most secondary metabolites from marine bacteria found so far are isolated from Streptomyces and Alteromonas species (Dobler et al., 2002). Zobell, (1942) is the first marine microbiologist worked on the microorganism in the world. The ocean has been described by bacteriologists as the “world’s target and most efficient septic tank” (Zobell, 1942). There are lots of work done on microbial natural products from number of authors like Burgess et al. (1999); Rosenfeld, (1947); Nair and Simidu, (1987); Burkholder et al. (1966); Faulkner, (2000); Teske et al. (2000); Wratten et al. (1977); Patil et al. (2001); Jensen and Fenical, (1994); Bennett and Bentey, (1989); Becerro et al. (1994); Strahl, et al. (2002); Jayanth, et al. (2002); Vairappan, (2003); Marwick et al. (1999); Jensen et al. (1998); Gorshkova et al. (2003); Boyd et al. (1999); Dobretsov an Qian, (2004); Barja et al. (1989); Peters et al, (2003); Rosa et al. (2000) and Chelossi et al. (2004) investigated the epibacterial diversity which was evaluated with both bacteriological and molecular approaches and a screening of epibiotic bacteria able to produce antibacterial metabolites was performed, whose identification was assessed by partial 16S rRNA gene sequencing.

Abraham (2004), Anderson et al. (1974), Wratten et al. (1977); Chellaram et al., 2004; Choudhury et al., 2003; Abraham et al., 1999 who worked on the discovery of novel antibacterial agents against fish pathogens.
Estimates of bacterial recoverability from environmental samples range from 0.01 to 12.5 % of the existing community (Ward *et al*., 1980). Improved recoverability of microbial colonies from marine sponges was reported by Olson (2000) and he had used sodium pyruvate and catalase as supplements. Spragg *et al*. (1997) have accounted antibiotics from surface associated marine bacteria using novel culturing technique. The most commonly utilized and successful supplements include catalase, sodium pyruvate and superoxide mutase. This agent acts to destroy free radicals and grow at higher O₂ tension. Hence, Martin *et al*. (1976) demonstrated that the presence of either catalase or sodium pyruvate in various non optimal media permitted the increased enumeration of injured and *Staphylococcus aureus* cells. Speck *et al*. (1975); Buker and Martin, (1982); Busta and Jeszeski (1963); Gonzalez *et al*. (2003); Flowers *et al*. (1977); Andrews and Martin, (1979); McDonald *et al*. (1983); Amin, and Olson, (1968); Harmon and Kautter (1976); Martin *et al*. (1977); Czechowicz *et al*. (1996); Heinments, (1953); Jensen *et al*. (1996) and Baird and Lee (1995) have worked on the enumeration of stressed cells on media could be increased by adding oxygen scavengers such as sodium pyruvate and catalase.

Pharmaceutical industry now accepts the world’s ocean as a major frontier for medical research. PharmaMAR (Spain and USA): has taken leading position in the development of drugs from sea. The four novel compounds were discovered by PharmaMAR such as, Yondelis, Aplidin, Kahalalide F and ES-285 in clinical trials and have a rich pipeline of preclinical candidates (Thakur *et al*. (2005). Benny *et al*. (1995) had shown the exploration of extraction of heparin like substances from the muricid gastropods *Chicoreus ramosus* and *C. virgineus*. Marine organisms provided numerous novel compounds with sensational multiple pharmacological properties (Rajaganapathi
et al. (2002); Premanathan et al. (1999); Jacobs et al. (1985); Turner (1996); Mayer and Gustafson (2000); Fernandez et al. (2002); Haeflner (2003); Faulkner (2000); Amador et al. (2003); Mayer and Lehmann (2001)). There are a copious number of authors like Look et al. (1986); Sharma et al. (2005); Ray et al. (2005); Mandal et al. (2005); Radika et al. (2005); Ahmed et al. (2001); Sertie et al. (2005); Perez and Rabanal, (2002); Martins et al. (2002); Mayer et al. (1998) who have done enormous works on the drug development for the analgesic and anti-inflammatory activity. There is however, sparse literature cited on the Central Nervous System (CNS) activity. Authors like Yousuf et al. (2002); Sukma et al. (2002); Yemitan and Adeyemi, (2005); Yusuf et al. (2002); Korkmaz and Wahlstrom (1997) have furnished many details regarding the CNS activity.

Besides to the antibacterial compounds isolated from the marine organisms, new agro-chemicals (insecticidal and Herbicidal) are also being isolated from the marine organisms. There is lots of works from the authors, Kabaru and Gichia, (2001); Llewellyn (2000); Fenical (1997); Zabriskie et al. (1986); Henricksona and Cardellina (1986); Selvam, 2002; Wagenen, 1998; Wright (1998); San-Martin et al. (1991); and Sayed, et al. (1997) on the isolation and characterization of novel insecticides from marine sources. Insect pests have been initially controlled with synthetic insecticides in the last fifty years (Ware, 1982 and Dorow, 1993); however, the search for new insecticides is a continuous process because there are problems of pesticide resistance and negative effects on non-target organisms including man and the environment as documented by Rembold (1984) and Franzen (1993).

Scientists like Elzen (2001) and Trisyono et al. (2000) have already evaluated the toxicity and new pesticide chemistries on beneficial arthropods. This is the reason for the
powerful need for such insecticides which are more powerful, with lesser side-effects and degradation reducing the chance to develop resistance against it (Kabaru and Gichia, 2001). Novel insecticidal classes such as polyhalogenated monoterpenes (San-Martin et al., 1991), polyhalogenated C-15 metabolites (Fukuzawa and Masamune, 1981; Watanabe et al., 1989), diterpenes (Ochi et al., 1991), phosphorylated derivatives (Okada et al., 1991, Wagenen et al., 1993) are reported from the marine sources. Many marine organisms including algae (Watanabe et al., 1989; San-Martin et al., 1991), sponges (Okada et al., 1991), corals (Shoji et al., 1993; He and Faulkner, 1991) and annelids (Okaichi and Hashimoto, 1962) are explored for their potent insecticidal properties. A number of plant families are known to produce alkaloids, phenols and oils which have been used as insect control since a long time (Nivsarkar et al., 2001). However, Kabaru and Gichia (2001) have already worked on screening the marine plants including mangroves, Rhizophora mucronata for insecticidal activities. Various workers including, Myers et al. (1993); Growesiss, (1974), Hamann et al. (1993) have documented that the Molluscs possess novel metabolites. So molluscs can definitely offer a wide array of chemicals for the discovery of novel agro-chemical agents.

Similar to insecticides, potent herbicides with novel mechanism of action are also in the way of development. There are copious chemical herbicides being used to abolish the weeds, in particular, the duck weed, Lemna minor. Dense populations of these weeds often form a green blanket on the water surface and Lynch (2004) has mentioned that numerous chemical weedicides are used to control the population of the duck weed, which includes, Fluridone, Diquat and chelated copper such as, Cutrine Plus, Algae Pro and Clearigate. Chemicals such as, Diquat dibromide and fluridone has proven to powerful controlling agents to limit the population of these water weeds. It is, in general,
argued that though the increased efficacy and safety have been developed in recent years, the agrochemical industries face growing criticism over the toxicity and residue problems associated with the use of chemical pesticides as cited by Huppatz (1990). Balogh and Anderson (1992) had argued that because many herbicides are toxic or biologically active by design, the use of synthetic pesticides for weed control has become a serious concern. Also, Piementel (1986) had stated that the judicious application of herbicides has become an integral part of agriculture. Sooner or later the weeds acquire resistance to the existing herbicides and thus the continued development of new and potent drugs for controlling weeds is required. However, Okuda (1992) had made a mention that the development of herbicides must always take into consideration the environmental pollution.

Blunt et al. (2005), Martin et al. (1979) and Faulkner (1977) have been conversed the chemical structures of natural product compounds are tremendously diverse and can be very elegant in their nature. Such diversity can present a challenge to the analytical or medicinal chemist attempting to unravel the mystery of the chemical structure of an unknown material presented. Nowadays, numerous chemicals compounds are being identified and characterized using various techniques. Numerous antibacterial compounds like Flexibilide / Sinulariolide are isolated from corals (Aceret et al., 1998), Indolequinones from snails (Fukuyama et al., 1998), and lectins from mussels (Tsukamoto et al., 1998).

During 2000, studies contributed to the antibacterial pharmacology of marine natural products. A novel acetylenic acid with antibacterial activity was isolated from the marine sponge Oceanapia sp. (Matsunaga et al., 2000). This fatty acid without a bromine atom that inhibited growth of the Gram-negative bacteria such as E. coli and
Pseudomonas aeruginosa as well as Gram-positive bacteria like Bacillus subtilis and Staphylococcus aureus. Three papers were published during 2000 on the anticoagulant properties of marine polysaccharides. Investigation on the in vivo anticoagulant pharmacology of the sulfated polysaccharide fucoidan was completed during 2000 by Thorlacius et al. (2000). The anti-inflammatory pharmacology of carvernolide, contignasterol, cyclolinteinone, oxenamide A, and an algal sterol glycoside was reported during 2000. Posadas et al. (2000) reported on the mechanism of action of cavernolide, a novel C\textsubscript{21} terpene lactone isolated from the sponge Fasciospongia cavernosa. Coulson and O'Donnell (2000) extended the in vivo pharmacology of contignasterol, a highly oxygenated sterol isolated from the sponge Petrosia contignata that appears to be as potent as nedocromil in inhibiting allergen-induced bronchoconstriction in vivo.

Reports on both central and autonomic nervous system pharmacology of marine natural products increased slightly over 1998 and 1999 (Mayer and Lehmann, 2000; Mayer and Hamann, 2002 and Mayer and Gustafson, 2006), with the 2000 studies involving the conantokins-G, T and R, the marine C. marmoreus conotoxin and α-Conotoxin MII and the halitoxins, lembheyne A and stolonidiol. Several studies extended the pharmacology of the conantokins and conotoxins, a family of small peptide toxins derived from the venom of Conus of the marine molluscs (Olivera, 1997).

The majority of natural product studies of the mollusca have been in the class of gastropoda. The interesting one is the predator cone shells of the genus Conus. This genus includes species that specialize in killing and eating fish and other organisms that prey on molluscs or worms. To be effectively hunters, these snails have evolved deadly mixtures of nerve toxins, small, conformationally constrained peptides of 10 to 30 amino acids that paralyze prey. These venoms or conotoxins, are targeted to various ion
channels and receptors. The conotoxins have provided neuroscientists and molecular pharmacologists with a rich source of new and exquisitely precise chemical probes for dissecting and manipulating ion channels and receptors and they are used in hundreds of physiological and pharmacological investigations (Mayers et al., 1993). Another important biochemical probe compound from the subclass Prosobranchia is the heterocyclic glycoside neosurugatoxin isolated from Japanese ivory mollusc Babilonia japonica. Neosurugatoxin is a reversible antagonist of acetylcholine receptors that was useful in characterizing two sub-classes, high and low affinity of this receptor (Ireland et al., 1993).

So far, the majority of natural product research in the Mollusca has been on the subclass Opisthobranchia, the shell-less snails. Most members of this subclass lack an external shell. The mantle covers the animal’s back and is often colorful, with flamboyant designs. Interest in the chemistry of opisthobranch molluscs has been based on the finding that many concentrate metabolites from their highly specialized diets and incorporate them into their own defensive strategies (Faulkner, 1998). Many biological studies of the natural products from the molluscs have therefore concentrated on potential ecological roles of the compounds. With the obtainable literature as a baseline, the present work deals with the exploration of bioactive substances from the coral reef associated macro and microorganisms.