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Marine Drugs: Implication and Future Studies

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Abstract: Natural product compounds are the source of numerous therapeutic agents. Recent progress to discover drugs from natural product sources has resulted in compounds that are being developed to treat cancer, resistant bacteria and viruses and immunosuppressive disorders. Many of these compounds were discovered by applying recent advances in understanding the genetics of secondary metabolism in microorganisms, exploring the marine environment and applying new screening technologies. Microbes have made a phenomenal/unique contribution to the health and well-being of people throughout the world. In addition to producing many primary metabolites, such as amino acids, vitamins and nucleotides, they are capable of making secondary metabolites, which constitute half of the pharmaceuticals on the market today (and provide agriculture with many essential products). A growing number of marine microorganisms are the sources of novel and potentially life-saving bioactive secondary metabolites. Here, we have discussed some of these novel antibacterial, antiviral, anticancer compounds isolated from marine-derived microbes and their possible roles in disease eradication and commercial exploitation of these compounds for possible drug development using many approaches.

Key words: Marinemicrobes, drugs, antibiotics, anticancer, antimicrobial

INTRODUCTION

The oceans cover over 70% of the earth's surface and contain an extraordinary diversity of life. Our interest in understanding the function of marine ecosystems has been accelerated in recent years with growing recognition of their importance in human life. Marine microbes have defined the chemistry of the oceans and atmosphere over evolutionary time. Thousands of different species of bacteria, fungi and viruses exist in marine ecosystems comprising complex microbial food webs. These microorganisms play highly diverse roles in terms of ecology and biochemistry, in the most different ecosystems and each drop of water taken from the ocean will contain microbial species unknown to humans in a 9:1 ratio (Colwell, 2002). The ocean represents a rich resource for ever more novel compounds with great potential as pharmaceutical, nutritional supplements, cosmetics, agrichemicals and enzymes, where each of these marine bioproducts has a strong potential market value (Faulkner, 2002). A lot of structurally and pharmacologically important substances have been isolated with novel antimicrobial, antitumor and anti-inflammatory properties (Bhadury and Wright, 2004). In many cases, natural products provide compounds as clinical/marketed drugs, or as biochemical tools that demonstrate the role of specific pathways in disease and the potential of finding drugs. In the areas of cancer and infectious disease, 60 and 75%, respectively, of new drugs, originate from natural sources. Raja *et al*. (2010) reported that new antibiotics active against resistant bacteria are required. Bacteria live on earth for several billion years. During this time, they encountered by range of naturally occurring antibiotics. To survive, bacteria developed antibiotics resistance mechanism (Hoskeri *et al*., 2010).

Natural products with industrial/human applications can be produced from primary or secondary metabolism of living organisms such as microorganisms. Among, them 50-60% are produced by plants (alkaloids, flavonoids, terpenoids, steroids, carbohydrates, etc.) and 5% have a microbial origin. Furthermore, from the 22,500 biologically active compounds that has been obtained so far from microbes, 45% are produced by actinomycetes, 38% by fungi and 17% by unicellular bacteria (Berdy, 2005). The increasing role of microorganisms in the production of antibiotics and other drugs for treatment of serious diseases has been dramatic. However, the development of resistance in microbes and tumor cells has become a major problem and requires much research effort to combat it.

Several reviews explore the development of marine compounds as drugs. There have been reviews on aspects of the chemistry and bioactivity of compounds from microbes, soft corals, cyanobacteria and microalgae,

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cyanobacteria and macroalgae, sponges, echinoderms, ascidians, fish, the sponge genus *Halichondria*, terpenes from the soft coral genus Sinularia and specific types of bioactivity associated with marine natural products have been reviewed in articles on anticancer drugs, agents for treating tuberculosis, malaria, osteoporosis and Alzheimer's disease, treatments for neurological disorders, anti-inflammatory agents anti anti-HIV compounds (Blunt *et al*., 2007).

Secondary metabolites, especially drugs have exerted a major impact on the control of infectious diseases and other medical conditions and the development of pharmaceutical industry. Their use has contributed to an increase in the average life expectancy in the USA, which increased from 47 years in 1900 to 74 years (in men) and 80 years (in women) in 2000 (Lederberg, 2000). As a great promising source for new natural products which have not been observed from terrestrial microorganisms, marine bacteria are being developed for the discovery of bioactive substances with new types of structure, with growing intensive interest. The achievements have been well reviewed, where many new antibiotics were obtained from microorganisms. With drug resistant strains of microbes appearing more frequently the biopharmaceutical industry has to move towards novel molecules in their development of new drugs. The oceans provide us with an opportunity to discover many new compounds, with over 13,000 molecules described already and 3,000 of them having active properties. Marine organisms have long been recognized as a source of novel metabolites with applications in human disease therapy.

HISTORY OF ANTIBIOTIC

Back in 1928, Alexander Fleming1 began the microbial drug an era. When, he discovered in a Petri dish seeded with *Staphylococcus aureus* that a compound produced by a mold killed the bacteria. The mold, identified as *Penicillium notatum*, produced an active agent that was named *Penicillin*. Later, penicillin was isolated as a yellow powder and used as a potent antibacterial compound during World War II. By using Fleming's method, other naturally occurring substances, such as chloramphenicol and streptomycin, were isolated. Naturally occurring antibiotics are produced by fermentation, an old technique that can be traced back almost 8000 years, initially for beverages and food production (Balaban and Dell'Acqua, 2005).

REASONS FOR DEVELOPING NEW ANTIBIOTICS FROM MARINE SOURCES

The WHO has predicted that between 2000 and 2020, nearly 1 billion people will become infected with *Mycobacterium tuberculosis* (TB). Sexually transmitted diseases have also increased during these decades, especially in young people (aged 15-24 years). HIV/AIDS has infected more than 40 million people in the world. Together with other diseases such as tuberculosis and malaria, HIV/AIDS accounts for over 300 million illnesses and more than 5 million deaths each year. Additional evolving pathogens include the Ebola virus, which causes the viral hemorrhagic fever syndrome with a resultant mortality rate of 88%. It is estimated that this bacterium causes infection in more than 70,000 patients a year in the USA (Balaban and Dell'Acqua, 2005). The Infectious Disease Society of America (IDSA) reported in 2004 that in US hospitals alone, around 2 million people acquire bacterial infections each year (http://www.idsociety.org/Content.aspx?id¼4682). *Staphylococcus aureus* is responsible for half of the hospital-associated infections and takes the lives of approximately 100, 000 patients each year in the USA alone (Hancock, 2007). New antibiotics that are active against resistant bacteria are required. The problem is not just antibiotic resistance but also multidrug resistance. In 2004, more than 70% of pathogenic bacteria were estimated to be resistant to at least one of the currently available antibiotics (Cragg and Newman, 2001).

Among them, *Pseudomonas aeruginosa* accounts for almost 80% of these opportunistic infections. They represent a serious problem in patients hospitalized with cancer, cystic fibrosis and burns, causing death in 50% of cases. Other infections caused by *Pseudomonas* species include endocarditis, pneumonia and infections of the urinary tract, central nervous system, wounds, eyes, ears, skin and musculoskeletal system. This bacterium is another example of a natural multi drug-resistant microorganism (Balaban and Dell'Acqua, 2005). Several viruses responsible for human epidemics have made a transition from animal host to humans and are now transmitted from human to human. In addition, the major viral causes of respiratory infections include respiratory syncytial virus, human parainfluenza viruses 1 and 3, influenza viruses A and B, as well as some adenoviruses. These diseases are highly destructive in economic and social as well as in human terms and cause approximately 17 million deaths $year^{-1}$ and innumerable serious illnesses besides affecting the economic growth, development and prosperity of human societies (Morse, 1997).

METABOLITES FROM MARINE MICROORGANISMS

Marine organisms comprise approximately half of the total biodiversity on the earth and the marine ecosystem is the greatest source to discover useful therapeutics. Sessile marine invertebrates such as sponges, bryozoans, tunicates, mostly lacking morphological defense structures have developed the largest number of

Table 1: Potential antimicrobial/anticancer compounds from marine organisms

Metabolites/compounds	Sources	Application	References
Euniatin B	*Fusarium* sp.	Antibacterial	Tsuda *et al.* (2003)
Modiolides A-B	*Paraphaeospheria* sp. N-119 (Separated from a marine horse-mussel)	Antibacterial	Okazaki *et al.* (1975)
SS-228 Y	*Chainia* sp.	Antibacterial	Christie *et al.* (1997)
Hypoxysordarin	*Hypoxylon croceum*	Antifungal	Liu *et al.* (2003)
Keisslone	*Keissleriella* sp.	Antifungal	Isaka *et al.* (2002)
Artemisinic acid	*Saccharomyces cerevisiae* (Host cell-rDNA process)	Antiparasitic	Martin *et al.* (2003)
Hypothemycin	*Aigialus parvus*	Antiparasitic	Chandran *et al.* (2003)
Shikimic acid	*Escherichia coli* (Host cell-rDNA process)	Antiviral	Rowley *et al.* (2003)
Halovirs A-E	*Scytidium* sp.	Antiviral	Feling *et al.* (2003)
Salinosporamide A	*Salinospora* sp.	Anticancer	Sudek *et al.* (2007)
Bryostatin	*Candidatus endobugula sertula*	Anticancer	Luesch *et al.* (2001)
Apratoxin A	*Lyngbya majuscule*	Antitumor	Jung *et al.* (2006)
Tylactone	*Sterptomyces venezuelae*	Antibiotics	Thakur *et al.* (2008)

marine-derived secondary metabolites including some of the most interesting drug candidates. In recent years, a significant number of novel metabolites with potent pharmacological properties have been discovered from the marine organisms.

Although, there are only few marine-derived products currently in the market, several marine natural products are now in the clinical pipeline, with more undergoing development (Rawat *et al*., 2006). Similar work has been conducted targeting uncultivable microbes of marine sediments and sponges using metagenomic-based techniques to develop recombinant secondary metabolites (Moreira *et al*., 2004). Marine bacteria are emerging as an exciting resource for the discovery of new classes of therapeutics. The promising anticancer clinical candidates like salinosporamide A and bryostatin only hint at the incredible wealth of drug leads hidden just beneath the ocean surface. Salinosporamide A, which is isolated from marine bacteria that is currently in several phase I clinical trials for the treatment of drug-resistant multiple myelomas and three other types of cancers (Ahn *et al*., 2007).

Microbes generally lack an active means of defense and thus have resulted in developing chemical warfare to protect them from attack. In addition, many invertebrates (including sponges, tunicates, bivalves, etc.) are filter feeders, resulting in high concentrations of marine viruses and bacteria in their systems. For their survival, potent antiviral and antibacterials had to be developed to combat any opportunistic infectious organisms (Table 1). It is hoped that many of these chemicals can be used as the basis for future generations of antimicrobials usable in humans.

MARINE NATURAL PRODUCTS BEING THE NEW SOURCE OF LEAD COMPOUNDS

In the past natural products have been a strong source for novel drug products, or have been a model for a drug that has made it to market (Cragg *et al*., 2006). The reasons for the strong showing of drug discovery from natural products can be attributed to the diverse structures, intricate carbon skeletons and the ease that human bodies will accept these molecules with minimal manipulation. The current trend within drug development is to find new precursor molecules from synthetic molecules as it is more cost-effective. This is because the techniques used with natural products include complex screening procedures that are time-inefficient and expensive.

In addition, a biological response from the mixture containing the compound may not be attributed to the chemical entity in question, but by another substance within the extract interfering with the screening procedure. The modern pharmaceutical shelves house a variety of compounds; however, there are a limited number of products on store shelves that are derived from a marine source. Historically, the first two compounds to make it to market from a marine source are Ara-A (Vidarabine®, Vidarabin®, Thilo®) and Ara-C (Cytarabine, Alexan®, Udicil®) (Patrzykat and Douglas, 2003). These compounds were isolated by Bergmann and Feeney (1951) and are still prescribed today. Ara-A is an anti-viral compound isolated from a sponge; Ara-C is isolated from the same sponge (Cryptotethya crypta) and has anti-leukemic properties. Natural products are becoming more popular again as marine organisms, both multi- and single-cellular, are an excellent resource with which to find novel chemical entities. Further, many chemical compounds isolated from marine organisms have great potential as antimicrobials or cytotoxic compounds due to the reliance of marine organisms on antimicrobial compounds or cytotoxic molecules as their innate defense mechanisms (Fig. 1a-e). There are currently over 3000 new substances identified from marine organisms in the past three decades, giving researchers a large pool of novel molecules from which to find new compounds to develop (Florida Atlantic University, http://www.science.fau.edu/drugs.htm).

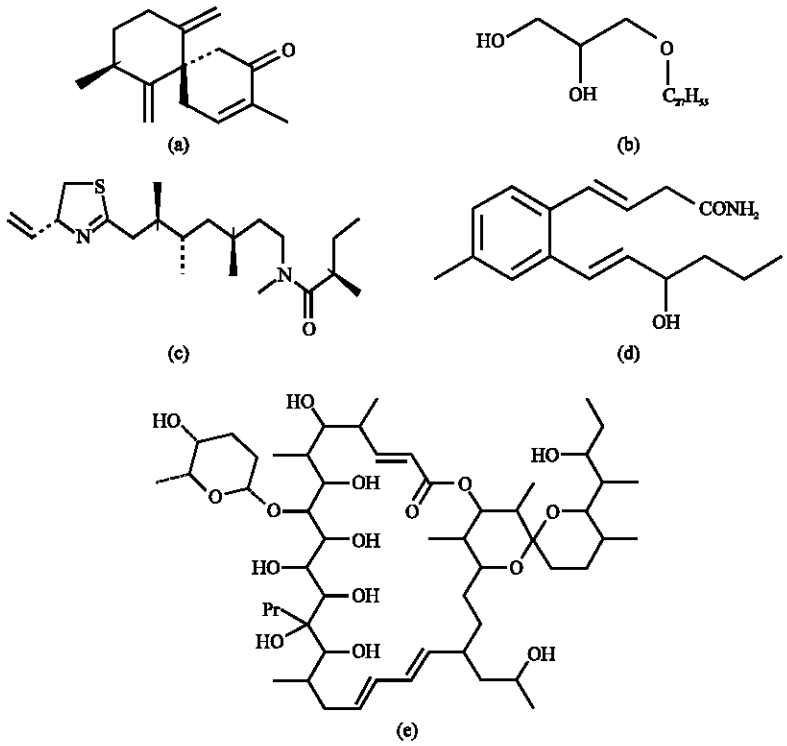

Fig. 1: Chemical structure of metabolites from marine sources. (a) convalutamines-bryozoans non-halogenated SesQuiterpene molluscs, (b) 3-heptacosoxypropane-1,2-diol sponges, (c) kalkitoxin-cyanobacteria, (d) lornemides A-actinomycetes aigialomycin D-fungi and (e) IB-96212-bacteria

For example, if properly developed, marine bacteria could provide the drugs needed to sustain us for the next 100 years in our battle against drug-resistant infectious diseases. Over the past century, the therapeutic use of bacterial natural products such as actinomycin D, daunorubicin, mitomycin, tetracycline and vancomycin has had a profound impact on human health, saving millions of lives. In the past 10 years (1997-2008), 659 marine bacterial compounds have been described. Marine fungi have proved to be a rich source of bioactive natural products. Most of these micro-organisms grow in a unique and extreme habitat and therefore they have the capability to produce unique and unusual secondary metabolites. To date, more than 272 new compounds have been isolated from the marine fungi and the number of compounds is on the increase (Tziveleka *et al*., 2003). According to the World Health Organization 100 million of people in the developing countries are affected by infectious diseases (Lee *et al*., 2009).

NEW DRUG FROM ENGINEERED MICROORGANISMS

Many chemicals and biological molecules that have been used as drugs are found in microorganisms, plants and animals. As these drugs are synthesized in only minute amounts, it is difficult to obtain them in suitable amounts. This is where metabolic engineering comes into play. The sequencing of genomes from cultivable microorganisms, chromosomal DNA is used to generate genomic libraries. Large genomic DNA fragments are directly isolated from the sample and cloned into suitable host vector systems (Fig. 2). Establishment of comprehensive gene libraries attempts to cover all genome sequences from sample, to gather as much information as possible on the biosynthetic machinery of a microflora.

Recent advances in our understanding on the metabolic pathways for the synthesis of these drugs together with the development of various genetic and analytical tools have enabled more systematic and rigorous engineering of microorganisms for enhanced drug production. Much rapid growth of microbial cells compared with higher organisms is another obvious advantage. Furthermore, metabolic engineering of microorgamisms can be performed more easily than mammalian and plant cells, which allows modification of metabolic pathways for the production of structurally more diverse analogs with potent biological activities, as in the cases of polyketides and non-ribosomal peptides

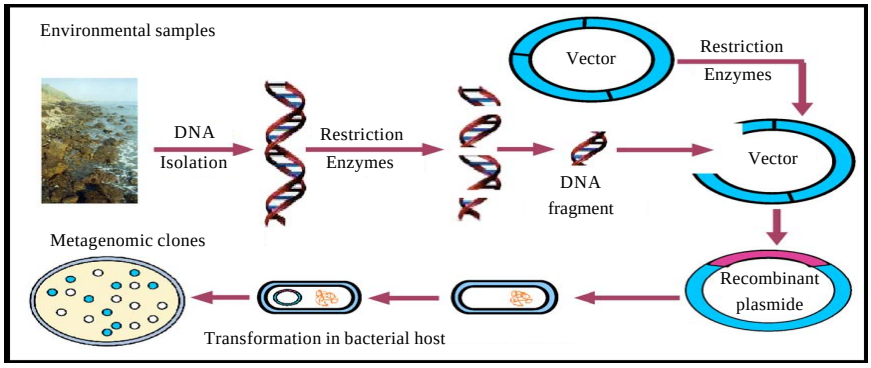

Fig. 2: Common schematic representation of rDNA (recombinant DNA) preparation from Marine environmental (Microorganisms) samples (Thakur *et al*., 2008)

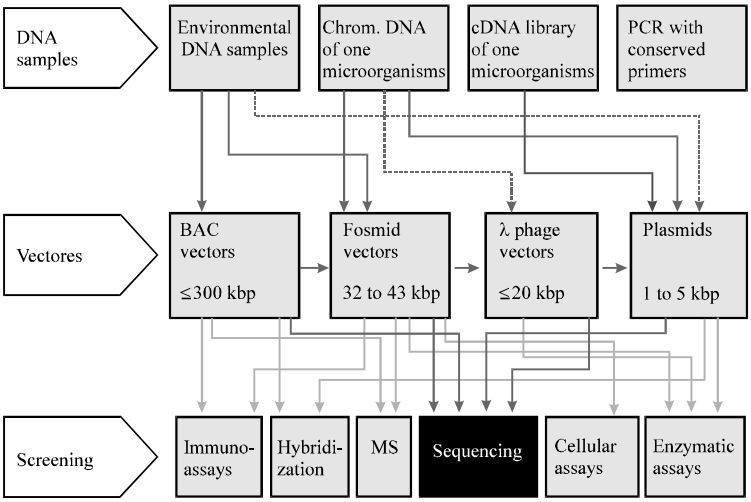

Fig. 3: Cloning strategies (Schweder *et al*., 2005)

(Minami *et al*., 2008). Although production of drugs at their final forms may be most desirable, biosynthesis of drug precursors is also favored experimentally and economically in several cases. High impact of microbial metabolic engineering toward the biosynthesis of drug precursors is well illustrated by the recent development of microbial systems.

Various drug molecules can be produced by employing metabolically engineered *S. cerevisiae* with appropriate heterologous genes using the same precursor synthesized by engineered *E. coli*. This is a good example of what metabolic engineering can do for the design and production of drug precursors that are difficult to obtain otherwise Biosynthetic capacity of marine Verrucosispora and Salinospora strains demonstrate that marine actinomycetes represent a new and potent source of bioactive secondary metabolites (De Vries and Beart, 1995). Shizuya *et al*. (1992) developed the bacterial cloning system Bacterial Artificial Chromosome (BAC) for mapping and analysis of complex genomes. Because of its high cloning efficiency and the stable maintenance of inserted DNA, the BAC system is able to facilitate the construction of DNA libraries of complex genomic samples but also provides a comprehensive representation of genome sequence of one organism. The ability to clone long stretches of DNA has become an important tool for genome analyses of uncultivated marine microorganisms (Fig. 3).

We may be able to incorporate the genes that produce the molecules scientists are interested in within plasmids of bacteria that we can easily grow. Drug production by metabolically engineered microorganisms has several advantages over total chemical synthesis or extraction from natural resources.

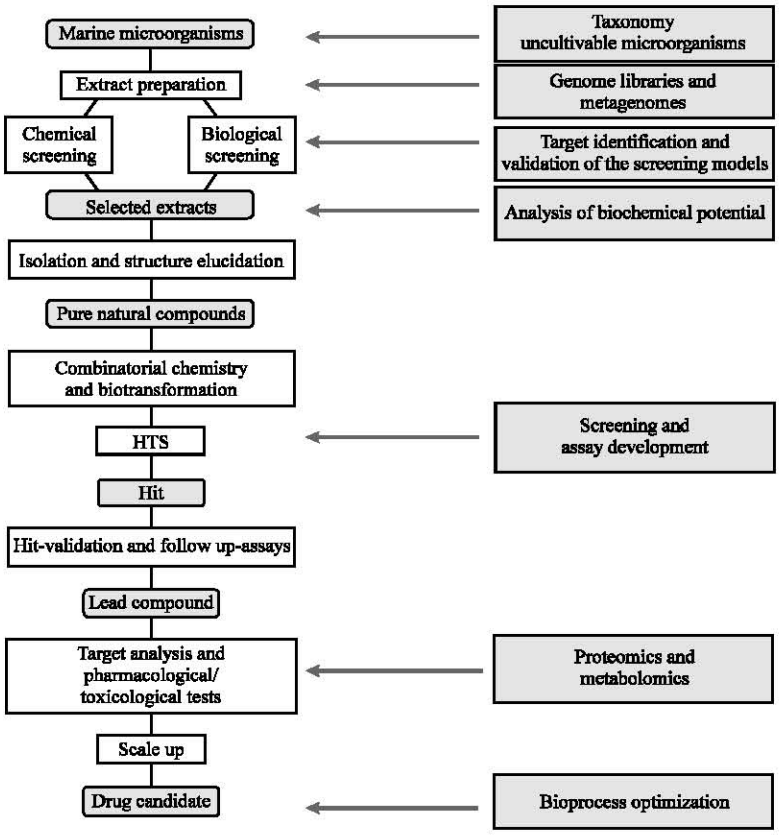

Fig. 4: Drug development process (Schweder *et al*., 2005)

IDENTIFICATION OF NEW ANTIMICROBIAL COMPOUNDS

Most of the antimicrobial compounds currently on the market were screened based on whole cell antimicrobial screening programs. By application of new genome-driven techniques more directed, target-based approaches are possible. These new screening strategies are directly coupled to potential drug targets, which have been identified by genome sequencing projects. Such antimicrobial targets are for example proteins that are essential for microbial growth or cell survival. The sequencing of the genome of a microorganism that has been identified as a potent producer of bioactive compounds allows the identification of the gene clusters involved in the pathways for the production of these natural compounds (Fig. 4).

SCREENING FOR NEW METABOLITES

The screening results depend on the quality of screening material, collection and storage of organisms, cultivation, extraction, storage of extracts and preparation of test samples. A directed (preselected) screening offers better chances of finding interesting metabolites than an undirected (blind) screening. Such a directed screening could be based on ecological observations on traditional experiences or search in novel organisms. Mode and solvent of extraction determine which substances are extracted. Solid phase extraction is a suitable method for automated sample preparation (Schmid *et al*., 1999). Chemical and physicochemical screening is the search for new chemical structures regardless of their biological activities. The chemical reactivity or physicochemical properties of the separated compounds are analyzed by spectroscopic methods (UV/VIS, MS, NMR) or by detection with special detection reagents in the TLC. The development of HPLC-DAD-MS systems allows the specific detection of single components in a complex mixture (e.g., an extract), regardless of the background of other metabolites. During biological screening test samples (extracts, fractions, pure compounds and compound libraries) are screened for their bioactivities *in vitro* and/or *in vivo*. In the case of extracts, active metabolites could be isolated by bioactivity-guided isolation processes. The finding of structurally known compounds (dereplication) in active extracts is possible. *In vitro* tests could be done on a molecular or on a cellular

level. An assay that requires careful interpretation but provides a lot of information per assay is ideal for marine natural products research. Tests on the molecular level are based, e.g., on receptor systems (identification of those compounds which bind to one receptor) or on enzyme systems (enzyme-catalyzed turnover rates).

Tests on the genome, transcriptome, or proteome level will become more and more important. Targets of high pharmacological relevance are G-protein coupled receptors, tyrosine kinase receptors, nuclear hormone receptors, ion channels, proteases, kinases, phosphatases and transporter molecules. The detection of a reaction on the molecular level could be done by biochemical assays (e.g., spectrophotometric measurement of the product of an enzymatic reaction), ligand binding assays (readout by labeling with a tracer) or functional assays (reporter gene assays quantifying the expression level of a specific reporter gene product, second messenger assays, two hybrid assays for measuring protein-protein interactions). Fluorescence-based assay technologies, isotopic labeling, colorimetry and chemoluminescence are very often used as detection methods. Cell-based assays are more complex and more physiologically relevant than tests on the molecular level. On the other hand, they are still labor intensive and more difficult to validate than molecular assays.

DEMERITS

With the potential of so many new compounds to combat bacteria, viruses and debilitating diseases such as alzheimers, osteoporosis and cancer why have marine sources not been thoroughly investigated before? The disclosure of compound, which organism it is isolated from and its structure become devalues leads to pharmaceutical companies losing the advantages. Many marine organisms are found in remote locations and can require large sums of money just to travel to and from these locations. Additional expenses including the specialized services of divers, submersibles and the personnel's safety and costs can become quite steep. An example of the prohibitive costs associated with collection of marine organisms is that a ship and submersible costs $14,500 per day (Hale *et al.*, 2002).

FUTURE OF MARINE SOURCES

The future looks bright for the pharmaceutical industry to develop new drugs from chemical structures isolated from marine sources. As of 2001 over 13,000 compounds, with 3000 of those denoted as being active compounds (those that have exhibited potential

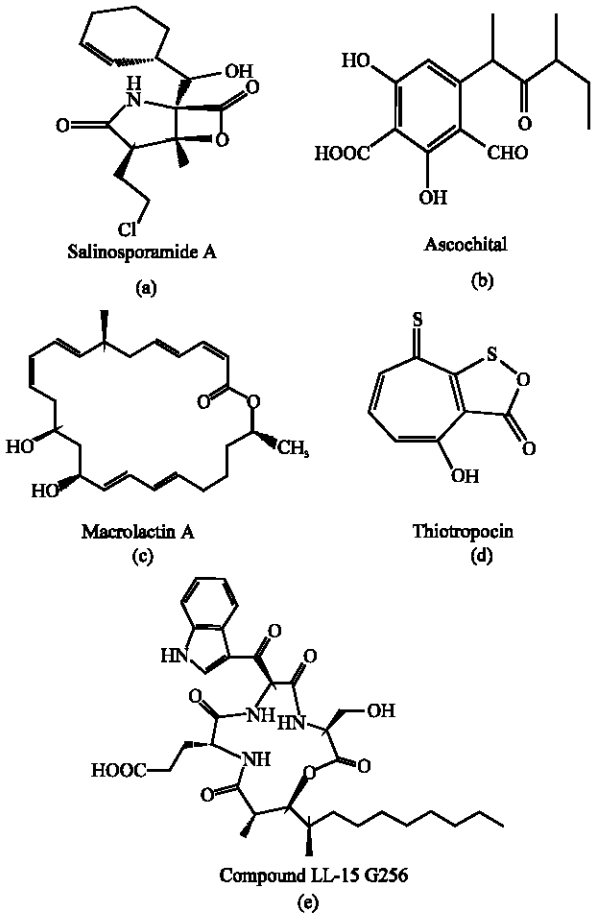

Fig. 5: Metabolites from marine microorganisms (Schweder *et al.*, 2005). (a) antitumor compound, (b) antibiotic compound, (c) antiviral compound, (d) anti-inflammatory compound and (e) antifungal compound

pharmaceutical effects), have had their chemical structures determined and documented (Fig. 5). The vast majority of these compounds are being developed in the hopes of treating cancer, tumour growth and leukaemia-over 67% of compounds isolated from marine origins have cytotoxic activity (Cragg *et al.*, 2006). Fifty years ago the search of drugs from marine sources was in its infancy and even though progress has been slow pharmaceutical companies are beginning to embrace the use of natural marine sources. In the research being conducted today, we also see a future trend towards marine natural resources as the number of papers reporting total syntheses or synthetic analogues are quite extensive. Partial and formal syntheses of compounds with their origins from marine sources are not documented in review in comparison, thus there are many more lead compounds with their origins from marine natural sources than

Table 2: Listed compounds derived from a Marine source and their activities (Cragg *et al.*, 2006; Florida Atlantic University, http://www.science.fau.edu/drugs.htm; http://www.findarticles.com/p/articles/mi_m0ISW/is_2001_Feb/ai_70777319/pg_1)

Metabolites/compounds	Sources	Application/activity	Stage R/D
Kainic acid	Digenea simplex	Anthelmintic	On market
Ara-C (cytarabine)	Cryptotethya crypta	Antileukemic	On market
Cephalosporins	Cephalosporium acremonium	Antibiotics	On market
Ara-A (Spongoadenoside)	Cryptotethya crypta	Antiviral	On market
Ziconotide	Conus magus	Antipain	Phase III
Ecteinascidin-743 (ET-743)	Ecteinascidia turbinate	Anticancer (alkylating agent)	Phase III
Dehydrodidemnine B	Aplidium albicans	Anticancer (prostate, bladder)	Phase II
GTS-10	Amphiporus lactifloreus	Alzhemer's disease	Phase II
Kahalalide F	Elysia rufescens	Antitumor	Phase I
Didemnim B	Trididemnum solidum	Antineoplastic/antiviral	Pre-clinical
Spongistatin 1	Hyrtios erecta	Antifungal	Pre-clinical
Manoalide	Luffariella variabilis	Anti-inflammatory, psoriasis	Pre-clinical

previously thought (Bourguet-Kondracki and Kornprobst, 2005). Investigators have a large amount of compounds to begin their investigations with and will provide the basis for future generations of drug products (Table 2). Anticancer drugs derived from marine sources have not yet been approved for market, yet a significant number are undergoing clinical trials and the future appears to hold a cancer treatment based on a marine natural source.

CONCLUSION

Natural products have played a significant role in drug discovery. Over the past 75 years, natural product derived compounds have led to the discovery of many drugs to treat human disease. Drugs developed from marine sources give us this hope and also give us novel mechanisms to fight some of the most debilitating diseases encountered today, including: HIV, osteoporosis, Alzheimer's disease and cancer. Although, the costs associated with developing drugs from marine sources have been prohibitive in the past, the development of new technology and a greater understanding of marine organisms and their ecosystem are allowing us to further develop our research into this area of drug development. This present review article will attempt to link these developments with some global issues and begin to present a convergent vision of many disparate views of the development of medicinal and biological agents from marine natural sources. This study is, in part, a commentary on finding a middle way, an as yet untrodden path in drug discovery, for the global health benefits of humankind from marine environment.

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