

Editorial

Drug Discovery, CAM and Natural Products

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Drug Discovery: Is it Relevant to Complementary and Alternative Medicine (CAM)?

This editorial is related to two papers in volume 1 issue 2 of *eCAM* and to others concerned with molecules derived from terrestrial and marine species (1–15). These papers focus on natural products, especially those derived from the sea. Therefore, it is appropriate to apply the contributions of these papers, since they can offer a different perspective. It is, indeed, a matter of great coincidence that these papers are being published at a time when *eCAM* is making extensive efforts to highlight this subject, which occupies an important place in biomedicine and has enormous potential. This situation in which the focus, at least of publications, is on animal products, is in marked contrast to that of botanicals and herbals—*qua* plant-derived molecules, the available literature on which may be considered immense and sometimes focused in highly specialized journals.

A recent issue of *Science* offers a veritable cornucopia of evidence concerned with new drugs, and it begins with an editorial entitled ‘Drug Discovery’ by Donald Kennedy Editor-in-Chief (16). This is followed by an introduction titled ‘Rethinking Drug Discovery (17) and a news essay, ‘Surviving the Blockbuster Syndrome; Orphan Drugs of the Future’ (18). Five reviews and viewpoints examine various aspects of molecular biology, organic chemistry and drug delivery systems (19–23).

If one explores the enormous wealth in this issue of *Science* in science’s next wave (www.nextwave.org), at least five presentations offer enormous potential for application (Bioprospecting beginning with ‘The Sweet Side of Venom and Practicing’ (24–28). This sojourn into the world of drug discovery is, in my opinion, an area pertinent to complementary and alternative medicine (CAM). It is not remote but is

closely related, relevant and highly visible, not to mention that it has rapidly increasing potential for wider distribution and understanding. This appears almost inevitable with the practice of western medicine shifting somewhat or, at least, bridging the divide between western and eastern medicine through the intervention of CAM. After all, many of these claims of healing have deep and everlasting recorded roots in the ancient world, most notably throughout Asia. The challenge will be to subject certain claims to the rigors of science and demand that conclusions be evidence-based (12). Otherwise, CAM will be unable to withstand the criticism of biologists and, sometimes, that of educated and skeptical public.

Historical Approaches to Antibiotics—A Template for CAM?

There is a current trend of discovery and applications of bioactive agents from natural sources. According to Grabley and Thiericke (29), natural products account for 30% of international drug sales. Although recombinant proteins and peptides have been accounting for an increasing amount of sales, the superiority of low-molecular mass compounds in human disease therapy remains undisputed, mainly due to more favorable compliance and bioavailability. To meet the demand for the thousands of test samples that must be submitted for high-throughput screening (HTS), it is essential to successfully compete with the rigors of combinatorial chemistry by developing new strategies in natural product chemistry. HTS enables the testing of a large number of samples. Therefore, new concepts that can generate large collection of compounds that possess improved structural diversity are desirable.

In the historical context and as a brief background, the discovery of antibiotics clearly ushered in a new approach for treating patients. It was entirely fortuitous—a byproduct of serendipity, a circumstance that scientists yearn for but from which they often do not benefit. In many respects, a template for CAM was being formed. Unlike this valuable discovery, and the currently emerging paradigm, the world of natural products has been awaiting more beneficial exploitation for several millennia. After all, what were people using as remedies

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long before Fleming's discovery of penicillin? In 1948, Japan was the third country, after the United States and the United Kingdom, to become self-sufficient in manufacturing penicillin (30). In addition to penicillin, there was an enormous amount of national exploratory research focusing on anti-infective, anti-cancer and agricultural antibiotics. Here is a summary, a brief chronology of discoveries. The first few antibiotics from Japan were colistin (1950), mitomycin C (1955), kanamycin (1957), bleomycin (1965), cefazolin (1969), amikacin (1972), piperacillin (1976), norfloxacin (1977), cefoperazone (1978), ofloxacin (1980), clarithromycin (1984), meropenem (1987), etc. Noteworthy antibiotic research on bioactive microbial products led to the discovery of agents beneficial to improving the human quality of life (QOL), e.g., pravastatin for hyperlipidemia and tacrolimus for atopic diseases. As an example among other nations, Japan will continue to maintain a high level of activity in exploratory research on beneficial chemotherapeutic agents during this century. The Japanese Society of Chemotherapy (JSC), established in 1953, has played a central role in evaluating novel agents including those introduced from other countries. The JSC is active in establishing guidelines for chemotherapy and in educating clinical scientists as well as evaluating chemotherapeutic agents both fundamentally and clinically.

The Oceans are a Rich Source of Natural Products that are Potential Medicinals—Natural Product Formulations Available in Europe for Psychotropic Indications

During the mid 20th century, the development of medical treatments for human disease was intimately connected with a

variety of products derived largely from the plant kingdom (31). Despite recent advances in utilizing chemically synthetic approaches to drug design and sophisticated structure-activity analyses, there continues to exist a great requirement in medicine for novel compounds with unique action mechanisms. While several thousands of structural analogs have been synthesized and tested, numerous gaps remain in the therapeutic armamentarium for psychiatric illnesses. A majority of the new drugs marketed for psychotherapeutic indications have only served as incremental improvements on existing medications. Significant discoveries have resulted primarily from analyzing natural products. Several valuable drugs have been isolated from plant and animal sources; these include aspirin, morphine, reserpine (the first antipsychotic), almost all antibiotics, digitalis, and anti-cancer agents such as vincristine, vinblastine, and Taxol.

Drugs from the Sea: Harvesting the Results of Aeons of Chemical Evolution

According to Wallace (32), despite recent developments in combinatorial chemistry that can rapidly generate thousands of new chemicals, the pharmaceutical industry still relies heavily on a staggering array of undiscovered possibilities from the natural environment. These could lead to the discovery of novel compounds that will surely extend the boundaries of our chemical research efforts. The terrestrial environment has been mined for compounds for many years, with great success. Currently, promising compounds are being tapped from the world's oceans. Many of these chemicals are structurally complex, which challenges modern organic chemists with unlimited approaches to mimic the synthetic versatility of nature. In

Table 1. Marine compounds under evaluation as potential drugs

Compound	Source	Activity	Status
Bryostatin I	Bryozoan, <i>Bugula neritina</i>	Anti-cancer	Phase II clinical trials
Ecteinascidin 743	Tunicate, <i>Ecteinascidia turbinata</i>	Anti-cancer: lung, breast and ovarian cancer, melanoma	Phase I clinical trials
Didemnin B (Aplidine)	Tunicate, <i>Trididemnum solidum</i>	Anti-cancer: central nervous system cancers, non-Hodgkin's lymphoma	Phase II clinical trials
Dolastatin 10	Opisthobranch mollusc, <i>Dolabella auricularia</i>	Anti-cancer	Phase I clinical trials
Halomon	Alga, <i>Portieria hommannii</i>	Anti-cancer	Advanced pre-clinical studies
Halichondrin B	Marin sponge, <i>Halichondria okadai</i>	Anti-cancer	Advanced pre-clinical studies
Discodermolide	Marine sponge, <i>Discodermia dissoluta</i>	Anti-cancer: immunosuppressant	Advanced pre-clinical studies
Jaspalkilonide (NCI)	Marine sponge, <i>Jaspis spp. or Dorypleres splendens</i>	Anti-cancer: antifungal	Pre-clinical studies
Manaloide	Marine sponge, <i>Luffariella variabilis</i>	Pharmacophore lead for numerous anti-inflammatory compounds	—
Dehydrodidemnin B	Tunicate, <i>Aplidium albicans</i>	Anti-cancer: prostate, lung, colorectal and central nervous system cancers	Pre-clinical studies
Kahalalide F	Mollusc, <i>Elysia rubefescens</i>	Anti-cancer: colon and prostate cancer	Pre-clinical studies
Mycaperoxide B	Marine sponge, <i>Mycale spp.</i>	Anti-cancer: ovarian and lung cancer	Pre-clinical studies
Cytophycin	Blue-green alga, <i>Nostoc spp.</i>	Anti-cancer	Advanced pre-clinical studies

Reprinted from Molecular Medicine Today, 3, Wallace R. W., Drugs from the sea: harvesting the results of aeons of chemical evolution, 291–299, 1997, with permission from Elsevier.

the future, these marine compounds are likely to yield entirely new classes of drugs which would be a valuable contribution to our ability to treat human disease. We are in need of such overtures, discoveries and innovations in the face of rising medical costs and the fact that a fraction of the general public (at least in the US) is underinsured and often disgruntled with modern-day, western medical practice. As we visualize a vaguely relevant situation of coexistence, a rather simple analogy is perhaps appropriate. Street markets are now offering complementary and alternative sources to the supermarket with its chilled atmosphere and speedy and efficient service. Perhaps we wish for something that has a long past and that offers, in many instances, equivalent or better service and assistance. CAM could possibly represent our street markets, whereas western medicine could be viewed as a super market.

Clearly, this brief sojourn reveals that medicine benefits immensely from the rich pharmacopoeia-products of our terrestrial and aquatic environments—both plants and animals. Although most medicines are derived from terrestrial plants and animals, ecologists estimate the number of species in the marine environment to be 0.5–10 million. Most of these are still waiting to be discovered, opening neither a Pandora's box nor a can of worms but an unfathomable array of newer cures. Several questions may be posed in this **new era of exploration**: Why marine organisms such as invertebrates? (32). Can problems related to synthesis and supply of marine natural products of pharmacological interest be resolved? So far, most marine secondary products are cellular toxins. What are the limits of marine biodiversity and how rapidly is this biodiversity being lost? Is it possible to provide a rational basis for discovering useful marine natural products by understanding the ecological interactions of organisms that compete with each other for food and space? What are the evolutionary connections between secondary metabolites from the marine world and the signaling pathways within our own bodies? Clearly, the papers included in eCAM provide some of the answers.

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