Medical Anthropology

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Natural Products from the Sea: Ethnopharmacology, Nutrition and Conservation

Introduction: Chemical Diversity and Evolution

The sea represents the most promising source of medicinal and nutritional natural products of the future. Traditional peoples have used natural products from the sea for medicinal and nutritional purposes for thousands of years. Natural products from the oceans are promising in part because of the incredible diversity of chemical compounds created by marine organisms. Since conditions in the marine environment are so different from those on land most classes of marine organism show molecules with unique structural features. Also, since many marine organisms are sessile they have evolved a wide variety of chemicals for defense, as well as communication and reproduction.

These unique molecular structures are precisely what are needed to help make new drugs and nutritional supplements. Terrestrial sources of drugs and nutritional products have been well explored, but less than one percent of marine species have been screened for organisms that contain or excrete novel compounds. Of the 27 diverse phyla of life, only 17 occur on land, yet 27 of the 27 occur in the ocean and so the largest proportion of biodiversity is in the ocean. As disease resistance to antibiotics and other drugs continues to increase, chemistry may not be able to meet the ever-increasing need for more efficient and more effective compounds. The oceans represent an untapped source of new medicines. (Pomponi 1999.)

Pharmaceuticals from the Sea

Despite the promise of marine natural products the pharmaceutical industry has been slow to explore this resource. However, smaller natural products firms, biotech companies and the National Cancer Institute (NCI) have begun exploring the oceans as a source of medical natural products in more depth and some products from this research are now in the clinical pipeline, with more in pre-clinical development. For more information see NCI's Natural Products Branch at http://dtp.nci.nih.gov. Some examples of compounds currently under study include:

- Bryostatin 1, isolated from the bryozoan *Bugula neritina*, an organism that attaches itself to the bottoms of boats off the coast of California, primarily for use as a treatment of melanoma, non-Hodgkin's lymphoma, and renal cancer.
- Dolostatin 10, a linear peptide derivative isolated from the sea hare *Dolabella auricularia* from the Indian Ocean, for use in the treatment of breast and liver cancers, solid tumors, and leukemia.
- AE941, a shark cartilage preparation, for use in treatment of various tumors.
- Ecteinascidin-743 (ET743) (Rinehart et al. 1981), a compound isolated from a Caribbean tunicate, has shown activity against ovarian (Valoti et al. 1998) and other tumors.
- Dehydrodidemnin B, isolated from Mediterranean tunicate *Aplidium albicans*, is being tested for its anticancer properties.
- An anti-inflammatory, manoalide, isolated from the Palauan sponge *Luffariella variabilis* and patented by the University of California for psoriasis. (Rinehart et al. 1981)
- Discodermolide, a metabolite of the deep-sea sponge *Discodermia*, which is immunosuppressive and cytotoxic, (Longley 1991) has potent antiproliferative activity due to its ability to stabilize microtubules, (Haar et al. 1996; and Kowalski et al. 1997). Novartis licensed it as a cancer treatment.
- Halichondrin B, isolated from the Japanese sponge *Halichondria okadai*, for melanoma and leukemia.
- Isogranulatimide, derived from a Brazilian tunicate, is a G2 checkpoint inhibitor that is shown to kill p53-tumor cells. It is also easy to synthesize which allows researchers to make analogues. (Roberge et al. 1998; Berlinck et al. 1998.)
- Debromohymenialdisine (DBH), one of several constituents of the common Palauan shallow-water sponge *Stylotella aurantium*, (Williams, Faulkner 1996) is easily synthesized and is being developed for treatment of osteoarthritis.
- An anti-inflammatory compound, *Pseudopterogorgia elisabethae*, extracted from the sea fan, is being used in an Estée Lauder skin care product, Resilience.

Production Methods

One major limitation to acquiring natural products from the sea versus land is the reduced accessibility of ocean environments. Bristol-Myers Squibb, one of the few major pharmaceutical companies to look into marine-derived compounds, recently returned licenses for eleutherobin, a compound isolated from a small Australian soft coral of the genus Eleutherobia, because they couldn't get enough of it. It is often difficult to obtain enough of a marine natural product to do a clinical trial, let alone produce it commercially. Pharmacological research in oceanic sources is slower and more difficult than land-based research. Property rights also continue to be a problem, following the Rio Convention. Discoveries made in another country's waters cannot be used. Some countries nowadays are controlling all research in their waters which prevents other researchers from gaining access. For example, the yield for [Ecteinascidin] ET743 is one gram per ton of tunicate. One ton will treat hundreds of people but this amount is hard to harvest due to conservation restrictions. (Valoti et

1998) The cost of research is also limited by the remote location of many marine resources. It sometimes takes researchers years to gain the funds and equipment to return to a remote ocean location which might harbor important natural products. For example, a ship and submersible costs $14,500 per day typically (Pomponi 1999).

Other methods being explored to produce marine drugs and natural products include aquaculture and chemical synthesis (Tsujii et al. 1988). The vast majority of compounds from the sea, however, are not easily synthesized. Many take 100 steps or more, compared to an average of 10 to 15 steps for medicinal compounds. And many of the marine bacteria are not culturable. These realities have marine researchers now looking to biotechnology's symbiosis and gene transfer (transferring genes into easily culturable organisms.) For many marine invertebrates the host itself isn't actually producing these compounds but instead relies on microbes (symbiosis) that can be easily cultured. (Harrigan et al. 1998, Bewley and Faulkner 1998.) Scripps Institute of Oceanography Center for Marine Biotechnology and Biomedicine http://www.sio.ucsd.edu/research/cmbb has just licensed a microbial anticancer agent with powerful effects on prostate cancer, as well as very potent anti-inflammatory and antiviral agents for use against herpes.

In contrast to drug companies, nutritional supplement companies do not face the need to extract active compounds from marine natural products since they generally sell them in their whole state. As a result, few are presently looking into chemical synthesis or biotechnology to increase production, although many are performing biochemical analysis of their products to determine which compounds are bioactive. Currently, a controversial topic in nutritional natural product research is the issue of standardization, the process of ensuring that a product has certain amounts of a marker compound that is active medicinally.

Marine nutritional supplements such as sea vegetables are also sometimes difficult and expensive to harvest in the wild. Yet, since they are harvested in their whole, unrefined state and usually from near-shore environments, the cost of harvesting and producing these products is much less than pharmaceuticals. Ecologically there is much less waste since the entire organism is used, instead of just extracting active compounds as occurs in the pharmaceutical industry.

Nutritional supplements are also increasingly being derived from marine microorganisms. Australian microalgae, presently used throughout Australia in the formulation of crucial live feeds for young aquaculture species such as oysters, prawns and abalone, is now being cultured for nutraceutical production internationally, supplying large markets in Asia and America. Australian manufacturers are currently supplying the nutraceutical market with betacarotene and other compounds such as omega 3 fatty acids derived from microalgae. (For more information on marine natural products research in Australia see www.marine.csiro.au)

Medical Anthropology

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Sea Vegetables

Besides drugs, the oceans are potential resources for a wide variety of non-drug nutritional natural products. These products are not regulated as drugs by the FDA but rather as dietary supplements and thus the cost of researching and developing them is much less. In general they are much less toxic than drugs, being consumed largely as they occur in nature rather than in refined or synthesized form. On the other hand they are less potent than drugs and thus are largely designed to promote health rather than for particular medical conditions. The following brief consumer guides to nutritional natural products were derived from www.mothernature.com and written in part by Craig Weatherby, myself and other content staff there.

Sea vegetables are perhaps the best known of these oceanic nutritional products. They have been used as human and animal food, medicines, and fertilizers for thousands of years by coastal peoples of Greece, China, Europe, and North America. Research has shown than many sea vegetables are in fact powerful promoters of health.

Sea vegetables are powerfully antiviral and antiparasitic. *Digenea* (Ceramiales; Rhodophycota) produces an effective vermifuge (kainic acid). Aqueous extracts from two red algae belonging to the Dumontiaceae have been found to inhibit the herpes simplex virus. Another red alga *(Ptilota)* produces a protein (a lectin) which preferentially agglutinates human B-type erythrocytes in vitro. Fucus contains fucoidin, a chemical (technically a short chained polysaccharide) that prevents cell proliferation and is strongly antiviral. Cultures that use it have a low incidence of viral diseases. (Stein and Borden 1984)

Sea vegetables are a source of many important minerals. In fact, 3-5 pounds of sea vegetables will fully mineralize (provide all essential minerals) an adult human for one year (Ryan Drum PhD, personal communication). Kelp is rich not only in iodine but various other nutrients, including enzymes, fiber, amino acids, vitamins including niacin and B12, and the minerals potassium, calcium, iron, and magnesium.

Sea vegetables are found to help prevent certain cancers. Inhibition of cancerous tumors in animals seems to be caused by long-chained polysaccharides. *Laminaria* and *Sargassum* species have been used in China for the treatment of cancer. Japanese scientists have shown that kelp may inhibit the development of breast cancer. Kelp may help remove heavy metals, radioactive particles, and other potentially toxic substances from the body. (Wong: 2000, Maruyama 1992) It is the alginates found in kelps and other sea vegetables that help to eliminate toxins in the body by binding with heavy metals, for example, and may help prevent cancers. Kelps and other seaweeds rich in iodine were shown in an animal experiment to suppress the thyroid's ability to absorb radioactive iodine, thus potentially preventing the organ from being injured by the harmful effects of radiation.

Sea vegetables are useful in reproductive medicine. Dry *Laminaria* stipes have long been used in obstetrics to dilate the cervix and were known as "*Laminaria* tents." The dry stipe slowly takes up water and expands. Such stipes are used in China for the insertion of intrauterine devices. (Stein and Borden 1984)

Thyroid dysfunction is often treated with marine algae such as kelp *(Fucus vesiculosus)* which was used in China nearly 5000 years ago for thyroid dysfunction. Scientists suspect there might be actual thyroid-hormone-like molecules present in marine algae. Kelp is also commonly used to counter goiter (enlargement of the thyroid gland, which is located on the neck) and underactive thyroid (hypothyroidism). The scientific rationale for these uses began in 1812 with the discovery in kelp of iodine, a mineral necessary for the body to produce thyroid hormones. A number of countries since the 1920s have added iodine to salt. This can effectively reduce goiter and other diseases associated with iodine deficiencies, but in some parts of the world these conditions remain serious public health problems that could be alleviated by consumption of kelp and other seaweeds. Because an underactive thyroid can lead to lethargy and weight gain, some people take kelp to boost energy and promote weight loss. Scientists in Hong Kong determined that, contrary to the common assumption that iodine deficiencies are rare in coastal cities, approximately 50% of both children and adults in Hong Kong had insufficient iodine levels. A dietary survey showed that seafoods and kelp were not commonly consumed. (Kung 1996)

Sea vegetables such as kelp have also been used topically as a folk remedy for minor burns, by moistening the strips in cool water and applying them to the skin. Alginates may help to promote the healing of burns and wounds. Alginate fibers in surgical gauze and bandages can help stop bleeding.

Sea vegetables such as kelp, along with green beans and common rue, contains substances that have a direct effect on the cardiovascular system and may be helpful in lowering blood pressure. (Chiu 1997)

Sea vegetables such as kelp are a source of mucilage, which can have a soothing effect on mucous membranes. Kelp may help to prevent or treat digestive disorders and bronchial congestion. Polysaccharide alginates found in kelp and other brown seaweeds have been widely used by the cosmetic and food industries for decades as emulsifiers, suspending agents, and stabilizers.

Sea vegetables can be eaten fresh or dried. Some people consume them as a side dish while they can also be used to flavor soups, stews, and salads. Sea vegetables are available in tablets, capsules, and liquids. The quality of sea vegetable products varies widely. Commercially available extracts are often deficient in the active compounds found in sea vegetables so they are best consumed in their whole state. Tinctures extract only 5% of the active compounds in Fucus, for example (Ryan Drum PhD, personal communication 1999). Drying does not damage sea vegetables (they are naturally dried every day on the beach.) Many cultures, particularly in Asia, have used sea vegetables both as food and medicine for much of history. Social science researchers have documented fluctuations in the harvest quantity and quality of sea vegetables in various cultures and pointed out ways to maintain sustainable usage patterns. From example, in the kombu harvest in Japan, this can include regulating harvesting by communal laws determined by the harvesters themselves, which often works better than bureaucratic regulation by government agencies. (Lida: 1998).

Toxicity of sea vegetables is low. However, long-term consumption of large doses of kelp may deliver excess levels of iodine to the thyroid, resulting in hyperthyroidism (over-active thyroid). Check labels of kelp supplements for iodine content since it can vary considerably depending upon species, growing conditions, and other factors. Kelp can also be high in sodium and may need to be taken with caution by anyone following a salt-restricted diet.

Chitin and chitosan are fibers derived from marine animals. Chitin is a polysaccharide, a string of sugar molecules, that naturally occurs in the hard outer shell of insects, shellfish such as crab, lobster, and shrimp, and marine coral. Chitin is chemically similar to cellulose and starch, the abundant plant fibers. It is used to make various other substances, including chitosan, which is derived from chitin by heating it with a chemical solution. Chitosan, has the advantage of being more soluble in water compared to chitin. Scientists have intensively investigated the properties and uses of chitin, chitosan, and their derivatives. Collectively they are the subjects of approximately 1,000 scientific studies and hundreds of patents. Most of this attention originated in Asia but in recent decades Westerners have begun to take chitin and chitosan as nutritional supplements and major corporations have jumped on the research bandwagon.

Chitosan has the unique ability to dissolve and bind fats and cholesterol in the stomach. Because chitosan is mostly indigestible, it can then prevent these lipids from being absorbed in the digestive tract. This can ultimately promote safe weight-loss and a reduction in cholesterol levels. Chitin and chitosan are also now being taken like acidophilus, FOS, and other supplements to speed the transit of foods through the digestive system and to promote the growth of beneficial live bacteria in the intestines. They can thereby improve digestion, cleanse the colon, and prevent diarrhea and constipation. More speculatively, chitin and chitosan may protect the liver, prevent or reduce tumors, heal ulcers, regulate blood pressure, and boost immune response. Chitin and chitosan have numerous industrial uses, in wastewater treatment; surgical sutures, wound dressings, and other medical applications; as a fertilizer and in animal feed; and in moisturizers, bath lotions, and other body care products.

Japanese researchers found that four weeks of chitosan supplementation reduced total blood cholesterol and caused a number of other beneficial effects on patients with kidney failure. (Jing, 1997) Chinese researchers recently confirmed antioxidant properties in chitin and chitosan compounds. Another recent study determined that a biological dressing made from chitosan was comfortable and efficient, and promoted the process of healing. (Drenda 1997)

Chitosan's primary mechanism of action is well established. It is known to differ from other polysaccharides in that it has a strong positive charge that lets it chemically bond with certain compounds, especially fats and cholesterol. Other mechanisms of action in the body are still being investigated. The ability to bond with fats and other substances is also the reason for many of chitin and chitosan's industrial uses. For example, spread on water chitin absorbs grease and other potentially toxic substances, which is why it is prominent in wastewater treatment processes.

Small amounts of chitin are found in mushrooms (where the substance was first identified in 1811) and yeast. The chitin and chitosan used to make nutritional supplements are derived from sources like crab shells and lobster shells, that are not

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eaten as foods. The most popular products are capsules and tablets ranging in size from 500 to 1,000 mg.

Chitin and chitosan are nontoxic and free of side effects, although they share the same precautions for safe use that apply to other types of fiber. Thus, to prevent intestinal blockage they should always be taken with plenty of water. Also, these supplements can bind with fat-based vitamins, such as vitamin E, and certain drugs, thus reducing these substances' absorption and effectiveness.

Shark Cartilage

Cartilage is a tough, elastic tissue found in the joints and other parts of the bodies of various organisms, including sharks and cows (bovine cartilage). Cartilage has a complex chemical makeup, including calcium, protein substances, carbohydrate mucopolysaccharides such as chondroitin, and collagen. Sharks are one of the prime natural sources of cartilage because their skeletons are made entirely of cartilage rather than bone.

Shark cartilage is taken to ease the pain and inflammation of arthritis, osteoarthritis, and other bone and joint ailments. Intestinal inflammations such as enteritis may respond to shark cartilage supplementation. Shark cartilage is also a popular alternative treatment for cancer, taken both to slow the growth of existing tumors and in smaller daily doses to prevent new cancers.

Canadian researchers found that a topical shark cartilage preparation had an anti-inflammatory effect when applied to the forearms of subjects, suggesting a potential role in the treatment of the common inflammatory skin condition psoriasis (Dupont 1998). Brazilian researchers using mice for subjects demonstrated a dose-dependent pain-relieving effect for shark cartilage.

A series of studies in 1998 have produced mixed results on the use of shark cartilage as an anti-cancer supplement. At high doses of as much as 1 g of shark cartilage supplement per kilogram of bodyweight, taken orally in three divided doses for six weeks, some studies have not found beneficial effects. However, this may be due to the low life expectancy of the study population. (Horsman 1998, Miller 1998)

Shark cartilage is known to contain glycoprotein compounds that strongly inhibit the process of angiogenesis, which is the growth of new blood vessels. Anti-angiogenic compounds have garnered increasing scientific attention among cancer researchers because these substances can potentially retard the growth of existing cancerous tumors by denying them the necessary blood-derived nutrients and oxygen. Inhibiting the development of new blood vessels may also account for shark cartilage's healing actions on joint, bone, and skin conditions. (Sheu 1998) Shark cartilage's effects may also be due to the immune-boosting action of its polysaccharide components. (Fontenele 1997)

Capsules and tablets range from approximately 250 to 800 mg. Shark cartilage is also available as a powder and "liquivial" extract. Prominent shark cartilage companies use cartilage from sharks caught for food, or from nonendangered shark species such as spiny dogfish. Shark steaks are a popular seafood but do not contain significant levels of cartilage.

Squalene

Squalene is an unsaturated hydrogen/carbon compound (a terpene) that is widely distributed in nature. It occurs in high concentrations in the oil derived from the livers of certain deep-sea sharks and in olive oil. Squalene is widely distributed in human tissues, most prominently in human sebum, the oily lubricant secreted by the skin's tiny sebaceous glands. Squalene supplements taken orally are a promising anti-cancer agent, although human trials have yet to be performed that could verify its usefulness in cancer therapy. As an ingredient in bodycare products squalene is an effective moisturizer, wrinkle remover, and wound healer. (see Kelly 1999 for a review of the clinical use of squalene.)

People take squalene to enhance the function of the immune system and to promote resistance to cancer. Researchers believe that squalene may be the constituent of olive oil that is responsible for the reduced cancer and mortality rates among populations, such as some traditional Mediterranean societies, that consume lots of olive oil. (Newmark 1997) Animal studies suggest that squalene can lower blood levels of fats and cholesterol, and a recent human study found that squalene promoted the effectiveness of a statin-type cholesterol-lowering drug. (Chan: 1996) Topically squalene is used to soothe and soften rough and dry skin and to promote the healing of wounds and sores.

A study found that mice fed diets rich in olive oil and squalene had significantly fewer lung tumors than those fed a corn oil control diet. (Smith 1998) Another recent animal study determined that squalene helps to protect against colon cancer. (Rao 1998) A recent review article noted that squalene appears to function on the surface of the skin as an antioxidant, capable of quenching singlet oxygen and protecting the skin from damage due to exposure to ultraviolet and other sources of ionizing radiation. (Kelly 1999)

Taken orally, squalene is thought to increase the oxygen supply to cells. It may also have hormone-regulating effects. Squalene is an intermediate in the body's synthesis of cholesterol. Animal studies suggest that squalene can prevent the spread of cancer by reducing the growth of blood vessels that supply solid tumors with the nutrients they need to grow. Sebum that is deficient in squalene allows skin to become rough and dry, and squalene that is applied to the skin is known to be quickly absorbed. Its effectiveness for wounds and sores may be due in part to its proven anti-bacterial action.

Supplemental squalene is available as a component of shark liver oil. Squalene is a popular ingredient in skin moisturizers and hand and body creams. Shark liver oil is the most concentrated source of squalene, although high amounts compared to other foods are also found in olive oil, wheat germ oil, and rice bran oil. Squalene is thought to be safe when taken at average doses.

Summary

The oceans represent the last frontier for humankind in so many ways, not the least of which is as a huge natural pharmacy. In this article I have shown how all types of researchers from chemists to biologists to anthropologists are helping to bring these oceanic natural products to our attention by discovering their mechanisms of action and methods of ecological use. Both pharmaceutical and nutraceutical products are available from the sea. While drugs are often more potent than nutraceuticals, they are often more expensive, more toxic and less ecological than nutritional supplements. By examining the usage of oceanic products by traditional cultures we can

...ilable ways to ensure their continued availability ...ice and medicine in industrialized societies.

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