PHARMACEUTICALS FROM ALGAE

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Contents

1. Introduction

The therapeutical use of algae has a long history with records dating back to the Chinese "Ben Cao" (herbal encyclopaedia) literature, Indian Ayurveda medicine and the *Materia medica* of Discurides (approx 70 AD). This use continues today. For example, various species of the red seaweeds *Chondria*, *Digenia* and *Alsidium* are used as antihelminthics against ascarasis in China. The active substance in *Digenia simplex* has been found to be α-kainic acid (Figure 2 (1)) and in *Chondria armata* it is domoic acid (Figure 2 (2)). The application of algae-derived compounds in modern medicine is however still limited and the main algae-derived chemicals in use remain the hydrocolloids such as agar, carrageenan and alginates that are used mainly in the food industry and in various industrial applications. In the last fifteen years other compounds from microalgae, such as the carotenoids ß-carotene and astaxanthin, and the long-chain polyunsaturated fatty acid, docosahexaenoic acid, have come into in commercial production and are sold as nutritional supplements and nutraceuticals.

Algae are proving to be a source of many potential new drugs and bioactive molecules. Living organisms have been a major source of new biologically active molecules for the pharmaceutical, animal health and agrochemical industries for much of this century. For example of the approximately 14 000 naturally occurring antibiotics known some 5500 are produced by actinomycetes and about 3300 by higher plants, with about 90 of these in current medical use. Detailed screening of algae (initially mainly of seaweeds) for bioactive molecules with antibiotic or other potential pharmaceutical applications began in the 1950s and has received greatly renewed attention in the last decade. This has led to the discovery of a very large number of novel compounds with diverse pharmacological and other biological activities. Several of these compounds are now being examined in more detail for potential medical applications. Given the great diversity of algae it is not surprising that they also display such a great chemical diversity.

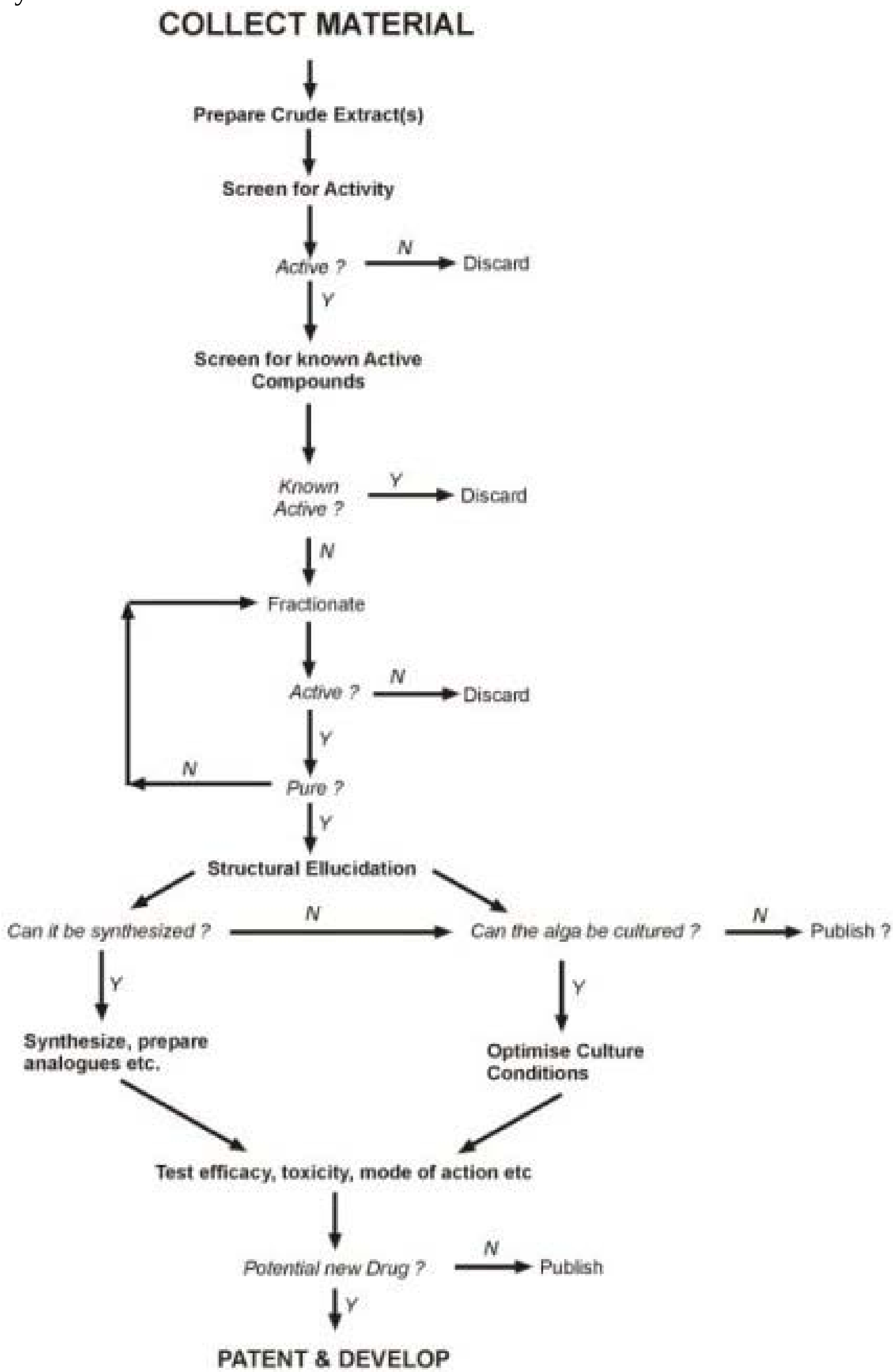

Figure 1. General scheme for the screening of algae.

The way bioactive natural compounds are searched for has changed significantly over the last 30 years. In the 1970s the approach to screening organisms for biologically active compounds shifted from the use of pure compounds in primary screens, to using "crude" extracts in preliminary screening and then using the bioactivity in the screen to direct the isolation and identification of the active compounds. This approach is shown in Figure 1, and was first applied on a large scale for the screening of marine algal and invertebrate extracts at the Roche Research Institute of Marine Pharmacology in Australia. The shift from terrestrial to marine organisms (see Marine Biotechnology) also led to an interest in algae, a group of organisms which had previously been almost totally ignored. Screening initially focussed on the seaweeds, however more intensive investigations of microalgae, especially cyanobacteria, began in the 1980s and they have proven to be a very rich source of novel bioactive compounds.

In the 1980s and 1990s a number of new technologies have led to the development of new miniaturised screens based on cell cultures, enzyme activities, and ligand-receptor binding. This miniaturisation and much greater sensitivity of these screens, combined with advances in robotics and computers, means that only very small quantities of extracts are needed. The minimum amount of organisms required to produce sufficient extract for screening has therefore been reduced from tens of kilograms to grams, thus extending the range of organisms which can be screened and reducing potential environmental damage from over-harvesting of natural populations. Furthermore, these developments have led to "high-throughput screening" (HTS) methods capable of screening thousands of compounds per day and into ultra-HTS methods capable of more than 100 000 assays per day.

Although algae produce many interesting compounds, there is little quantitative information available on how algae rate as sources of bioactive molecules compared to other plants, microbes and animals. Testing of extracts for cytotoxicity in preclinical screens conducted by the National Cancer Institute in the USA showed that about 0.1% of the almost 2000 samples of algae screened showed activity. This is a significantly lower "hit" rate than with marine invertebrates. The "hit" rate is much better in screens for antibiotic activity. For example one study has reported *in vitro* antibacterial activity in 10% of the 300 freshwater algae screened, and another observed antifungal activity in about 5% of the 532 marine and freshwater species screened. Similarly over 1000 strains of laboratory-cultured cyanobacteria, when screened for fungicidal activity using several species of fungi and yeasts, have shown activity in more than 10% of the samples against one or more of the test organisms. Unfortunately these *in vitro* screens do not translate directly to *in vivo* activity, an essential prerequisite for antibiotics with clinical potential. The only study where such data is available showed that although 36.1% of the 2017 algal extracts screened showed *in vitro* antibacterial activities only 4.9% showed *in vivo* activities, and these were mainly against Gram-positive bacteria.

This review cannot cover all of the compounds from algae that have shown activity in pharmacological and other screens, but rather highlights the chemical diversity and the diverse activities found. These active compounds may lead to new drugs, serve as chemical models for new drugs, or have application as research tools in studying physiological and biochemical processes.

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Biographical Sketch

Michael Borowitzka is Associate Professor of Phycology at Murdoch University, Perth, Western Australia. He obtained his PhD at the University of Sydney. This was followed by time as a post–doctoral fellow at the Scripps Institution of Oceanography, La Jolla, California and as a Queen's fellow in Marine Science at the Australian Institute of Marine Science, Townsville. He then headed the biology section of the Roche Research Institute of Marine Science in Sydney searching for new bioactive compounds from marine organisms. Later, as Senior Scientist at Roche Algal Biotechnology he helped develop the commercial culture of *Dunaliella salina* as a source of beta–carotene before joining Murdoch University in 1983. Michael is the past President of the Asia Pacific Society for Applied Phycology, on the editorial board of several journals, including the *Journal of Applied Phycology*, *Botanica Marina* and *Coral Reefs*, and the President of the WA Branch of the Australian Biotechnology Association.