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Fungal Endosymbionts of Macroalgae: Need for Enquiries into Diversity and Technological Potential

TS Suryanarayanan[1]* and JA Johnson[2]

[1]Vivekananda Institute of Tropical Mycology (VINSTROM), RKM Vidyapith, Chennai 600004, India
[2]Department of Biology, University of New Brunswick, 100 Tucker Park Rd, Saint John, NB, Canada

Recent studies reveal that ascomycete fungi establish an endosymbiotic association with marine algae [1-4]. Akin to the endophytes of terrestrial plants in causing disease-free infections in their hosts, these fungi need to be studied with the same zeal as endophytes as they are a promising source of novel bioactive metabolites. The Fungal Endosymbionts of Macroalage (FEM) elaborate molecules exhibiting antitumour, antioxidant, anticancer, antimicrobial, antifungal, cytotoxic and other bioactivities [5-7]. An *Aspergillus* sp. harboured by a marine alga elaborates antibiotics effective against methicillin resistant bacteria [8]; FEM isolated from macroalgae of North Atlantic produce antibacterial and larvicidal metabolites [7]. A *Fusarium* endosymbiont of a marine alga off the coast of southern India formed antimalarial metabolites showing activity against blood stage *Plasmodium falciparum* [9]. The synthetic ability of FEM is further substantiated by Flewelling et al. [10] who showed that a *Penicillium* endosymbiont of *Fucus spiralis* produced epiepoformin, phlyllostine, patulin and cladosporin-a metabolite that has not been previously reported as a product of this genus. Although these few studies identify FEM as a promising source of novel metabolites of pharmaceutical and agricultural importance, a number of challenges confront us before their potential could be fully realized. We identify some roadblocks which need to be addressed.

The study of macroalgae as an ecological niche for endosymbiotic fungi is inchoate emphasizing the need to obtain information on the diversity and distribution of these fungi in different algal hosts found in different geographical locations. The limited studies so far indicate that marine-derived fungi, rather than the true marine fungi, occur as endosymbionts and genera such as *Aspergillus*, *Cladosporium* and *Penicillium* are common endosymbionts of taxonomically unrelated and geographically disparate macroalgae [6,7]. Although this picture may change with more sampling (hardly a few macroalgae of the hundreds of different species have been screened for their fungal endosymbionts), it would be of interest to investigate such a wide host range of a few fungal genera. It appears that the chemical diversity of FEM could be higher than species diversity since the same fungal species isolated from different algae exhibit different bioactivities [7]. Since FEM are analogous to the better investigated endophytic fungi of terrestrial plants, studies on endophytes could serve as model to gain insights into FEM. Culture and molecular approaches have been used to understand endophyte species diversity [11-13], seasonal shift in species composition [14], and life style shift with time [15]. Similar studies on species diversity of FEM as influenced by season, environment, host species, host tissue type and host age are needed to obtain the necessary background information for the bioprospecting exercise to be successful. Endophytes influence the ecological fitness of their host plants by enhancing their tolerance to abiotic [16,17] and biotic [18-20] stress. In this context, information on the influence of FEM on the growth and ecological fitness of various macroalgae would improve their sustainable production especially since macroalgae are used as feedstock for biofuel and for the production of industrial biomaterials [21,22]. Although macroalgae themselves elaborate a wide array of bioactive metabolites [23], it is not known if any of these metabolites are the products of the endosymbionts (as has been observed for some marine sponges [24]) or whether they play a role in selecting the endosymbiont assemblage. Furthermore, isolating an endosymbiont capable of producing the industrially important metabolite elaborated by its algal host would lead to easier production and extraction of the chemical since culturing of the endosymbiont and manipulating the conditions for maximum yield is more tractable than direct extraction of the metabolite from the alga.

Prospecting for natural products is fraught with the problem of extracting and identifying known chemical structures after a great deal of effort and expense. As the library of extracts from FEM sources grows so does the need to prioritize which of these extracts will be considered for further investigation. The use of metabolomics by way of Nuclear Magnetic Resonance (NMR) and Liquid Chromatography Tandem Mass Spectrometry (LC-MS) could help resolve extracts with the same or similar compounds [25-29] facilitating rapid progress in FEM research.

Bioactivity profiles can also help overcome the issue relating to redundant results where bioactivity against selected human pathogens is the primary method of screening for potential novel compounds when testing crude extracts and fractions from FEMs. By creating a profile of extract activity against a large number of bacteria and comparing this to the activities of known antibiotics where the mode of action has been characterized [30,31], it would be possible to focus efforts on unique crude extracts containing potentially novel metabolites.

The number of efflux pump inhibitors continues to grow for both Gram + [32,33] Gram – bacteria [34,35] and fungi [36,37]. Using FEM extracts along with sub-lethal doses of known antibiotics against pathogens with acquired resistance may help identify compounds not acting directly as antibiotics but vested with the ability to augment the therapeutic potential of antibiotics. Advances in this field will help when investigating the potential for FEM extracts. Although it is not known how the secondary metabolism of FEM is regulated *in vivo*, microarray technology Brazas and Hancock [38] could reveal if and how FEM metabolites down or up regulate their algal host genes and *vice versa*. Growing fungi under different culture conditions may

***Corresponding author:** TS Suryanarayanan, Vivekananda Institute of Tropical Mycology (VINSTROM), RKM Vidyapith, Chennai 600004, India, Tel: +91 9791186036; E-mail: t_sury2002@yahoo.com

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induce the expression of silent gene clusters governing secondary metabolism resulting in the production of metabolites not detected under normal culture conditions [39,40]. As an illustration of this, an *Aspergillus terreus* isolated from *Ulva lactuca* formed antialgal metabolites only in the presence of NaCl in the growth medium [41]. It is therefore necessary to screen FEM under different culture conditions and also by co-culturing them with their algal hosts and other marine microbes to get a more complete picture of their metabolite spectrum.

Lastly, endophytes of terrestrial plants are also a potential source of novel enzymes of industrial importance [42,43]. Very few studies exist on the catalytic potential FEM have in this regard. According to Thirunavukkarasu, et al. [44], FEM are a good source of the therapeutic enzyme L-asparaginase which is used in the treatment of acute lymphoblastic leukaemia. FEM could also be screened for various algal polysaccharide modifying enzymes to obtain tailor-made oligosaccharides which find use in enhancing the resistance of crops against their pathogens [45].

In summary, even the very few studies on FEM indicate that these are fungi with extraordinary synthetic potential. Investigations to screen different algal species from different parts of the world for these endosymbionts and their bioactive metabolites would pay rich dividends. It is urged that efforts to screen marine habitats for drugs by different countries include these fungi in their agenda for a more complete bioprospecting exercise.

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