HIGH SPECIALIZED DETECTORS OF BIOACTIVE MOLECULES FROM MARINE ENVIRONMENT

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Abstract

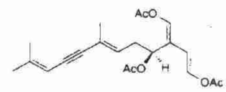
The paper concerns the detection of bioactive marine products moving from their natural functions. This study is directed to sessile and slow moving organisms which, being apparently unprotected, use to be chemically armed. In particular, the main attention is focused on Mediterranean molluscs, such as opisthobranchs, which are able to feed specifically on sponges and algae, well known to be protected by chemicals against most of other marine predators. Following the sluggish track left from such invertebrates, chemists have isolated oustanding, chemically different molecules, usually involved in a number of ecological endowments. But is the utility of these compounds confined at such functions or may they be involved in more general processes? In other words, can the ecological role be only the first evidence to move interest in investigating, extensively, further bioactivities? This is the current challenge.

Key-words : porifera, algae, mollusca, natural products

How is it possible to find out bioactive molecules from natural sources? There are a few different strategies. Sometimes, by a random approach, compounds are first isolated and then submitted to a series of aimed tests, sometimes, by guided screening, bioassays are used to select natural products with specific activities. Both strategies demand a huge amount of work and only big, well organized groups have proved able to detect potentially feasible applications for human purposes. Fortunately, there is a third way that directly aims at selecting molecules which play a vital role in the organisms where they are contained. In the ecological approach, the expensive requirement of preliminary tests is replaced by field observations of the marine habitat. In fact, it is surprising how sessile organisms are able to survive in an environment where the competition for existence is extreme. Sponges, soft corals, bryozoans, algae have conquered, in spite of their apparent fragility, a lot of marine space. Analogously, other organisms, moving very slowly, seem to be completely unprotected against aggressive predators. This is the case of opisthobranchs which being molluscs without the mechanical protection of the shell, which is either reduced or completely absent, have elaborated a series of alternative defensive strategies including the use of chemicals (1-4). In this communication we will present several evidences in order to prove the ability of opisthobranchs to detect bioactive molecules from their preferred dietary sources, mainly sponges and algae. In our idea, the ecologically relevant properties of such compounds can be the starting point for further studies which, moving from the comprehension of their natural function and mechanisms of action, aim at finding out more general (pharmacological or technological) applications.

The subclass Opisthobranchia belongs to the class Gastropoda and is split in eight orders: Cephalaspidea, Anaspidea, Saccoglossa, Thecosomata, Gymno-somata, Notaspidea, Acochlidiacea, Nudibranchia (5). With a major reference to our studies, the present report summarizes the main results obtained on species belonging to the orders Sacoglossa and Nudibranchia. From an evolutionary point of view, the order Sacoglossa is highly intriguing for the presence of ancestral species, hardly protected by relic shell, together with evolute animals showing reduced or completely absent shell. On the contrary, all slugs of the order Nudibranchia are totally naked. The survival of the organisms of both orders depends on chemicals able to repel common marine predators. A relevant topic is to establish how the molluscs are able to procure their protective weapons.

Almost all saccoglossans are herbivores with a diet based mainly on green algae. The Mediterranean *Ascobulla fragilis* is an infaunal mollusc possessing a hard shell. The taxonomical collocation of *A. fragilis* between Cephalaspidea and Saccoglossa is matter of debate. Although its external feature shows strong likenesss with cephalaspideans, the mollusc is, analogously with other conchoid sacoglossans, closely associated with the rhizoid of the green alga *Caulerpa prolifera*. In fact, two conchoid molluscs, *Oxynoe olivacaea* and *Lobiger serradifalci*, live on the leaves of the same alga where they are well concealed by their green colour. All three molluscs are chemically protected by the algal metabolite caulerpenyne [**1**], but the defensive strategy of conchoid species appear much more sophisticated than that of *A. fragilis*. In fact, all these molluscs are able to increase the toxicity of 1 by transforming it into the more toxic oxytoxin-1 [**2**] and oxytoxin-2 [**3**] (6, 7). But, besides secreting toxic mucus, *O. olivacea* and *L. serradifalci* are able to autotomize part of their body. In particular, as molested, *Oxynoe* uses to lose the tail, whereas *Lobiger* sacrifices some dorso-lateral appendages, generally called cerata. Moreover, whereas oytoxin-2 is present only in the mucous secretion of the three molluscs, oxytoxin-1 is accumulated by *O. olivacea* and by *L. serradifalci* specifically in the autotomizable parts of their body. All these molluscs are highly specialized detectors of bioactive molecules. The partial structure of **1**, characterized by a dienolacetate, will be found in other algal metabolites sequestered by aconchoid saccoglossans belonging to the superfamily Elysioidea (8): the compound **4** sequestered by *Elysia translucens* from *Udotea petiolata*; the compound **5** by *Bosellia mimetica* from *Halimeda tuna;* the compound **6** by *Thuridilla hopei* from *Derbesia tenuissima. T. hopei* is, also, able to modify **6** to its dihydroderivative **7**. All these molecules exhibit a masked conjugated 1,4-dialdehyde which, probably is responsible of a series of biological properties (cytotoxic, antimicrobial and feeding-deterrent activity (9)). A strong parallelism was found studying a number of other sacoglossans from Caribbean Sea: *Ascobulla ulla, Oxynoe antillarum, Lobiger souverbiei, Elysia subornata, Elysia patina, Elysia tuca, Elysia nisbeti* (10).



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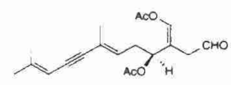

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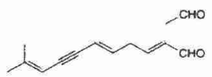

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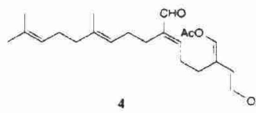

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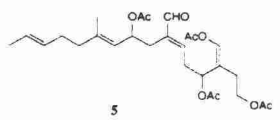

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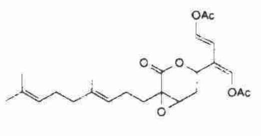

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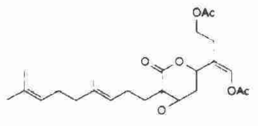

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On the basis of the above evidence we have identified a first group of highly specialized detectors of bioactive molecules. But, moving to other saccoglossan species we observed (11, 12, 13) that these molluscs, from both Mediterranean and Caribbean Sea, are also able to construct *de novo* bioactive molecules completely absent in their algal diet. Generally, these compounds, some of which are summarized in Table 1, display a polypropionate skeleton containing a α - or γ-pyrone ring. They possess obvious deterrent properties against marine preda-