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A preliminary catalogue of natural substances of opisthobranch molluscs from western Mediterranean and near Atlantic.*

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SUMMARY: A list of opisthobranch molluscs species from the western Mediterranean and nearby Atlantic is presented. These species have natural products that are of interest because of their chemical structure, origin and/or function in benthic ecosystems. This review contains data on the origin and activity of these molecules, collection sites of the animals, and their bibliographic references. A discussion of these subjects is also included.

Key words: Natural products, opisthobranch molluscs, chemical ecology, western Mediterranean, near Atlantic.

RESUMEN: CATÁLOGO PRELIMINAR DE SUBSTANCIAS NATURALES DE MOLUSCOS OPISTOBRANQUIOS DEL MEDITERRÁNEO OCCIDENTAL Y ATLÁNTICO PRÓXIMO. — Se presenta un listado de especies de moluscos opistobranquios del Mediterráneo occidental y Atlántico próximo, que poseen substancias naturales de interés por su estructura química, su origen y/o su función en ecosistemas bentónicos. Se incluyen datos sobre el origen y la actividad de estas substancias, los lugares de procedencia de los animales estudiados, las referencias bibliográficas relacionadas, así como una discusión sobre los mismos.

Palabras clave: Substancias naturales, moluscos opistobranquios, ecología química, Mediterráneo occidental, Atlántico próximo.

INTRODUCTION

Natural products from marine organisms have attracted the attention of scientists from different fields during the past decades. In molluscs, their "utility" was well known since the time of Dioscorides and Pliny (The Elder) (CAPROTTI, 1977). The first objective of the chemical study of natural products was the characterization of metabolites; then, terrestrial toxins and interesting medical molecules were studied. Research on marine toxins began in the 60's, when an important systematic development in marine animals took place. Multidisciplinary research, involving biological and ecological implications of chemicals, began later, in the early 80's.

Special attention has always been paid to new molecular structures from the sea, and particularly from opisthobranch molluscs (SCHEUER, 1977, 1981, 1982; SCHULTE *et al.* 1980; SCHULTE and SCHEUER, 1982; FAULKNER, reviews from 1984 to 1991, 1988b; CIMINO *et al.*, 1986a: KREBS, 1986; KARUSO, 1987), and also to topics such as biosynthesis (GARSON, 1989). On the other hand, ecological and biological studies of defence in opisthobranchs have been made (THOMPSON, 1960a, b, c, 1976; THOMPSON and BROWN, 1984; EDMUNDS, 1966, 1968, 1987; STASEK, 1967; HARRIS, 1971, 1973; ROS, 1976, 1978; GARCÍA-GÓMEZ *et al.*, 1991). However, few studies have re-

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ported data on both biology and ecology of the chemical phenomena: FENICAL *et al.*, 1979; SCHEUER, 1987; SODANO, 1981; FAULKNER and GHISELIN, 1983; BAKUS *et al.*, 1986; HAY and FENICAL, 1988; PAUL, 1988; CIMINO and SODANO, 1989, CIMINO *et al.*, 1990c; PAUL *et al.*, 1990, SCHEUER, 1990. These studies are mainly about few species or reduced groups.

Exclusively chemical reviews usually provide little information on the origin and activities of metabolites, sampling area or habitat of the species. We have found it useful to compile a list in which chemistry and biology are integrated, thus rapidly facilitating the location of species, natural products, origin, activity, area and related bibliography. This catalogue of opisthobranch species (from the western Mediterranean and nearby Atlantic) includes all the species known to us in which secondary metabolites have been studied. Few sterols and their derivatives are given, but petrosterol and some others which were considered of interest. External secretions have been included when detected.

A new approach in the study of marine natural products has just begun in the Mediterranean Sea, thus correlating community structure with chemical activities (URIZ *et al.*, 1991).

Secondary metabolites are non-nutritional chemicals controlling the biology, coexistence and coevolution of species (TORSSELL, 1983). They can be basically classified according to their biological function into allomones, kairomones and pheromones (BROWN, 1975). Allomones are chemical substances involved in interactions between different species which benefit the producing organism (the best-known being used as repellents); kairomones, in contrast to allomones, benefit the receiving organism; and pheromones are chemicals used for intraspecific communication.

METHODS

The catalogue is structured into five columns. The first column lists the species names following CERVERA *et al.* (1988), and the publication name (in brackets) if different from the current name. Natural substances and secretions are placed in the second column. In the following columns the list includes the origin of substances, the activity type, and the region from where the animals studied came.

Origin codes:

B. *De novo* biosynthesis.
S. Sponges.
A. Algae.
C. Cnidaria.
O. Other opisthobranchs.
-. Unknown origin.
?. Hypothetical origin.

The first case includes species that are able to biosynthesize *de novo* their own allomones (*Dendrodoris* spp., *Doris verrucosa, Tethys fimbria, Cyerce cristallina*). In the rest of the cases, metabolites have been shown to be obtained from the prey species (sponges, algae, cnidaria or even other opisthobranchs). In the areas studied there are no data on metabolites obtained from bryozoans or ascidians, although they certainly exist in other regions (CARTE and FAULKNER, 1983; PAUL *et al.*, 1990).

Activity codes:

The codes used in the catalogue are:

I. Ichthyotoxicity.
D. Feeding deterrence.
P. Alarm pheromone.
C. Cytotoxicity for *Artemia salina.*
T. Tumor promoter.
A. Autotoxicity (toxic to the same animal).
R. Regenerator for *Hydra.*
N. Neurotoxic for mice.
U. Unspecified toxicity.
-. Unknown activity.
?. Hypothetical activity. (Often based on similar chemical structure to other molecules of proven activity).

Experimental tests have usually been carried out with the isolated compounds to ascertain their biological activity. Detailed explanations about the tests can be found in the literature. The most commonly employed tests are ichthyotoxicity and antifeedant or feeding deterrence tests. The rest of the codes refer to certain species in which, for chemical or biochemical reasons, a specific activity was suspected and tests were made for confirmation. In other cases, no experiments or tests have been made, or no results have been reported (in the list, represented by the symbol-). Negative results are represented as "no" followed by the activity code.

Area codes:

The regions studied were divided into five parts. Zone 1 includes the western Italian coast, Thyrrenian

Sea and Ionian Sea. Zone 2 includes the southern coast of France (in the Mediterranean) and the north-eastern part of the Iberian Peninsula (Catalan and Valencian coasts and the Balearic Islands). Zone 3 includes the southern Iberian Peninsula. Zone 4 includes the Cantabrian Sea (Asturian, Cantabrian and Basque coasts, in the northern part of the Iberian Peninsula); also in this area we include some references from the south of Britain (which were considered interesting for the subject of this paper). And, finally, zone 5 includes the Canary Islands.

Not all the geographical areas used in this list have been studied equally. Italian coasts are the better studied (60 % of listed products) because one of the most productive marine natural products research groups is located at the I.C.M.I.B.-C.N.R. in Naples (Italy).

LIST OF SPECIES

Opisthobranchs (references)	Substances	Origin	Activity	Area
Order Cephalaspidea				
Acteon tornalitis (72, 128, +)	purple secretion	–	U	4
Scaphander lignarius (31, 47, 82)	yellow viscous secretion	–	–	4
	lignarenone-A	–	P?	1
	lignarenone-B	–	P?	1
Philine aperta (129, 130, 133, *)	sulphuric acid	–	D?	4
	hydrochloric acid	–	D?	4
	acid secretion	–	–	2
Gastropteron meckeli (*)	compound related to 4-cholesten-3-one	–	–	2
Philinopsis depicta (*Aglaja depicta* 26, 29, 33, 47, 102, 138, *)	aglajne-1	O	–	1
	aglajne-2	O	–	1
	aglajne-3	O	–	1
	adenosine	–	–	1
	haminol-A	O	P	1
	haminol-B	O	P	1
	compound related to 4-cholesten-3-one	–	–	1
Bulla striata (33, 138)	aglajne-1	–	–	1
	aglajne-2	–	–	1
	aglajne-3	–	–	1
Haminoea hydatis (31, 102)	haminol-A	–	P	1
	haminol-B	–	P	1
Haminoea navicula (31, 47, 102)	haminol-A	–	P	1
	haminol-B	–	P	1
Akera bullata (31, 99, 102)	purple secretion	–	–	4
	? haminol	O?	–	1
Order Anaspidea				
Aplysia depilans (50, 70, 97, 128)	inking secretion	–	D?	1
	white secretion	–	–	4
	dictyol A	A	–	1
	dictyol B	A	–	1
	dictyol C	A	–	1
	dictyol D	A	–	1
	pachydictyol A	A	–	1
Aplysia dactylomela (70, 78)	inking secretion	–	D?	1
	trioxygenated diterpene	–	P	5
Aplysia fasciata (*A. limacina*, 70, 91, 122, 128)	inking secretion	–	D	1
	purple secretion	–	–	4
	white secretion	–	–	4
	polyhalogenated monoterpenes	A	–	1
	4-acetyl-aplykurodin-B	–	I	1
	aplykurodinone-B	–	I	1
Bursatella leachii (32, 107)	bursatellin	–	–	1
Order Sacoglossa				
Oxynoe olivacea (43, 56, 101, 123)	oxytoxin-1	A	I, D, C, R	1
	oxytoxin-2	A	–	1
Cyerce cristallina (54, 56, 136)	cyercene-A	B	I, R	1
	cyercene-B	B	I	1
	cyercene-1	B	–	1
	cyercene-2	B	I	1
	cyercene-3	B	I	1
	cyercene-4	B	I	1
	cyercene-5	B	–	1
Placida dendritica (137)	placidene-A	B?	I, no R	1
	iso-placidene-A	B?	I, no R	1
	placidene-B	B?	I, no R	1
	iso-placidene-B	B?	I, no R	1
Order Notaspidea				
Tylodina perversa (13, 29)	?bromo compounds	S	–	1
Umbraculum mediterraneum (35, 38, 76)	umbraculumin-A	–	I	1
	umbraculumin-B	–	no I	1
	umbraculumin-C	–	I	1
Pleurobranchus membranaceus (108, 126, 127, 128, 129, 131, *)	sulphuric acid	–	D?	4
	hydrochloric acid	–	D?	4
	acid secretion	–	D?	2
Berthella plumula (125, 126, 128)	acid secretion	–	D?	4
	sulphuric acid	–	–	4
Berthella aurantiaca (*)	acid secretion	–	–	1, 2, 4
	purinic compounds	–	–	4
Berthella stellata (*)	acid secretion	–	–	4
Berthella ocellata (*)	acid secretion	–	–	1
Pleurobranchaea meckelii (108, *)	acid secretion	–	–	1, 2
Order Nudibranchia				
Trapania lineata (*)	compound related to 4-cholesten-3-one	–	–	2
Hypselodoris villafranca (*H. gracilis*, 4, 6, 19, 56, 71)	longifolin	S	I, D	1, 2, 4
	dendrolasin	S?	D	4
	nakafuran-9	S	D	1, 4
	tavacfuran	S?	D	4
	agassiziin	S?	–	4
	iso-nakafuran-9	S?	D	4
	ent-furodysinin	S?	I, D	4
	iso-dehydrodendrolasin	S?	–	4
Hypselodoris tricolor (4, 56, 71)	longifolin	S?	I, D	4
	dendrolasin	S?	D	4
	nakafuran-9	S	D	4
	tavacfuran	S?	D	4
	agassiziin	S?	–	4
	iso-nakafuran-9	S?	D	4

Opisthobranchs (references)	Substances	Origin	Activity	Area
	ent-furodysinin	S?	I, D	4
	iso-dehydrodendrolasin	S?	–	4
Hypselodoris webbi (*Glossodoris valenciennensi*, 4, 6, 22, 56, 73)	longifolin	S	I, D	1, 2, 3
	nakafuran-9	S?	D	1, 2
	iso-tavacfuran	S?	–	2
Hypselodoris coelestis (*Glossodoris tricolor*, 22, *)	furoscalarol	S	D	1
	deoxoscalarin	S	D	1, 2
	epi-deoxoscalarin	S?	–	2
Hypselodoris cantabrica (4, 56, 71)	longifolin	S?	I, D	4
	dendrolasin	S?	D	4
	nakafuran-9	S	D	4
	tavacfuran	S?	D	4
	agassiziin	S?	–	4
	iso-nakafuran-9	S?	D	4
	ent-furodysinin	S?	I, D	4
	iso-dehydrodendrolasin	S?	–	4
Chromodoris luteorosea (4, 44, 56, 77)	luteorosin	S?	I	1, 4
	12-*epi*-aplysillin	S?	I	1
	12-*epi*-12-deacetyl-apysillin	S?	I	1
	macfarlandin A	S?	I	1, 4
	norrisolide	S?	I	4
	polyrhaphyn-C	S?	I	4
	chelonaplysin-C	S?	I	4
Chromodoris purpurea (4, 56)	luteorosin	S?	–	1, 4
	macfarlandin	S?	–	1, 4
	norrisolide	S?	–	4
Chromodoris krohni (4, 56)	luteorosin	S?	–	1, 4
	macfarlandin	S?	–	1, 4
	norrisolide	S?	–	4
Doris verrucosa (2, 3, 17, 30, 37, 76,106, *)	verrucosin-A	B	I, T	1, 2, 4
	verrucosin-B	B	I, T	1, 2, 4
	xylosyl-MTA	B	–	1, 2, 4
	pyruvic acid oxime	S	–	1, 2
Discodoris atromaculata (13, 14, 19, 20, 25, 42, *)	petrosterol	S	–	1, 2
	polyacetylenes	S	–	1, 2
	petroformyne 1	S	C	1
	petroformyne 2	S	C	1
	petroformyne 3	S	C	1
	petroformyne 4	S	C	1
Discodoris stellifera (*Anisodoris stellifera*, 59, 108, *)	acid secretion	–	–	1, 4
Discodoris indecora (96)	fasciculatin	S	D, no I	3
Platydoris argo (*)	compound related to 4-cholesten-3-one	–	–	2
Phyllidia pulitzeri (22, 138)	isocyanosesquiquiterpenes	S	–	1
	axisonitrile-1	S	I, no D	1
Dendrodoris limbata (5, 21, 22, 23, 27, 36)	polygodial	B	D, A	1, 2
	olepupuane	B	–	1, 2
	7-deacetoxy-olepupuane	B	–	1, 2
	drimane esters	B	–	1, 2
	euryfuran	B	–	1, 2
Dendrodoris grandiflora (5, 19, 28, 36)	polygodial	B	D	1
	olepupuane	B	–	1
	7-deacetoxyolepupuane	B	–	1
	6-ß-acetoxyolepupuane	B	D	1
	drimane esters	B	–	1
	fasciculatin	S	–	1
	microcionin-1	S	–	1
	microcionin-2	S	–	1
	microcionin-3	S	–	1
	microcionin-4	S	–	1
	furospongin-1 acetate	S	–	1
	prenylated chromanols	S	–	1
	C-21 furanoterpene	S	–	1
Doriopsilla areolata (*)	sesquiterpenes related to *Dendrodoris*	–	–	2, 4
	compound related to 4-cholesten-3-one	–	–	2, 4
Tethys fimbria @ (39, 46, 48, 52, 53, 55, 56, 95)	PGE_2	B	no I	1
	PGE_2-1, 15-lactone	B	I	1
	PGE_2-1, 15-lactone-11-acetate	B	–	1
	PGE_3	B	no I	1
	PGE_3-1, 15-lactone	B	I	1
	PGE_3-1, 15-lactone-11-acetate	B	I	1
	$PGF_2\alpha$-1, 15-lactone-11-acetate	B	no I	1
	$PGF_2\alpha$-1, 15-lactone fatty acid esters	B	no I	1
	$PGF_3\alpha$-1, 15-lactone-11-acetate	B	no I	1
	$PGF_3\alpha$-1, 15-lactone fatty acid esters	B	no I	1
	PGA_2-1,15-lactone	B	–	1
	PGA_3-1,15-lactone	B	I	1
Armina maculata (79, 80, 81)	verecynarmin A	C	–	2
	verecynarmin B	C	–	2
	verecynarmin C	C	–	2
	verecynarmin D	C	–	2
	verecynarmin E	C	–	2
	verecynarmin F	C	–	2
	verecynarmin G	C	–	2
	preverecynarmin	C	–	2
	cembrene-C	C	–	2
Janolus cristatus (121)	janolusimide	B?	N	1
Flabellina affinis (18, 19)	polyhydroxylated steroids	C	–	1
Flabellina lineata (*Coryphella lineata*, 18, 19)	polyhydrodylated steroids	C	–	1
Cratena peregrina (*Hervia peregrina*, 18, 19)	polyhydroxylated steroids	C	–	1

Numbers under each species name correspond to the numbered list of references
(* = unpublished results from the author at the I.C.M.I.B.).
(@ = PG means prostaglandins).
(+ = the purple secretion of *A. tornatilis* has not been found by N. Yonow, p.c., who studied more than 1000 specimens).

DISCUSSION

Natural products of opisthobranchs are derived from the three basic secondary metabolic pathways (acetate, propionate and mevalonate). Some examples are given in Fig. 1.

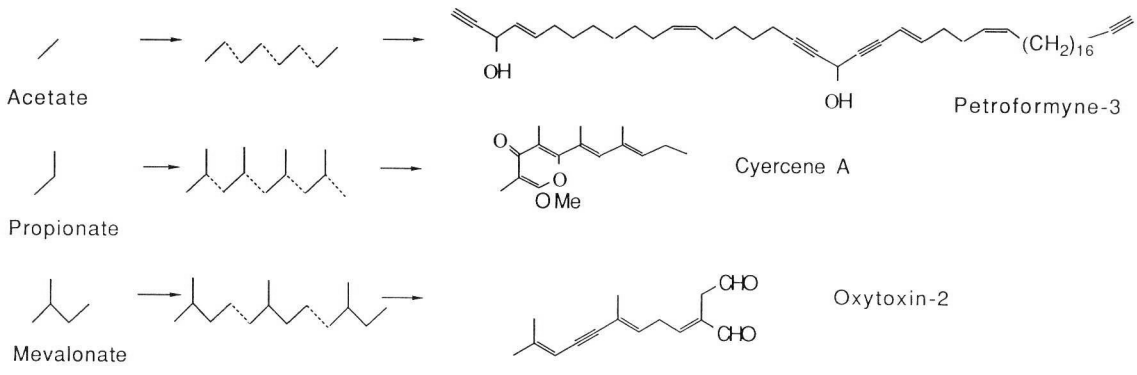

FIG. 1. — Some examples of opisthobranch natural products from the three basic secondary metabolic pathways.

Other opisthobranch compounds have mixed biogenesis, for instance verrucosins (mevalonate and glycerol) and haminols (acetate and pyridine). Dendrodorididae and Chromodorididae compounds are basically derived from the mevalonate path (sesquiterpenes, diterpenes, etc.). Substances having dietary origin come from the secondary metabolism of the prey species, where they can have different functions, but in some cases they are modified by the molluscs, as in the sacoglossan *Oxynoe olivacea* (see the list for references). The function of products related to 4-cholesten-3-one, widely distributed in many different species, is unknown but it is probably correct to assume that it is a result of oxidation of sterols. Acid secretions are found mainly in the order Notaspidea, and also in some Cephalaspidea (such as *Philine aperta*).

Although results are still scarce, natural substances could be used in taxonomical considerations (KARUSO, 1987). Results obtained indicate a strong correspondence between chemical products and taxonomy, showing the enormous potential of these studies. Some examples are discussed. *Hypselodoris* and *Chromodoris* species show a clear relationship with some sponges on which they feed (*Dysidea* spp., *Aplysilla* spp., *Spongionella* spp.), accumulating and efficiently using their metabolites for defence. In the Mediterranean *Hypselodoris* species, the molecular structure of these compounds presents 15 carbon atoms, and in Mediterranean *Chromodoris* species, 20 carbon atoms. Other studies on Chromodorididae from different areas also shown the presence of dietary-derived diterpenoids, sesquiterpenoids, and other terpenoids (SCHULTE *et al.*, 1980; HOCHLOWSKI *et al.*, 1982, 1983; MOLINSKI and FAULKNER, 1986 and BOBZIN and FAULKNER, 1989). *Doris verrucosa* (see references in the list) and some *Archidoris* species (studied in other areas by ANDERSEN and SUM, 1980; GUSTAFSON *et al.*, 1984; GUSTAFSON and ANDERSEN, 1985; FAULKNER *et al.*, 1990) have structurally similar compounds (terpene glycerides). The same kind of drimane sesquiterpenoids (see listed references and also OKUDA *et al.* (1983) for other areas), are found in different species of the family Dendrodorididae, such as *Dendrodoris limbata* and *Doriopsilla* spp.

Few cases are known in which species are independent of their diet for their defence, in the sense that they can *de novo* biosynthesize their allomones (*Dendrodoris* spp., *Doris verrucosa, Tethys fimbria, Cyerce cristallina;* see the list for references). Nevertheless other examples are known in different geographic areas, such as *Navanax inermis* (navenones A-C; SLEEPER and FENICAL, 1977; FENICAL *et al.*, 1979; SLEEPER *et al.*, 1980; *Archidoris montereyensis* and *A. odhneri* (terpenoidic acid glycerides, references quoted above), and *Placobranchus ocellatus* (related to symbiotic associations, IRELAND and SCHEUER, 1979).

The origin of secondary metabolites is not only interesting chemically, but is also ecologically very useful to demonstrate prey-predator relationships when the products are dietary-derived. Natural products of many opisthobranch species come from a known prey (Table 1). For instance, the sacoglossan *Oxynoe olivacea* transform some products from the green algae *Caulerpa prolifera;* species of the genus *Hypselodoris* obtain products from sponges of the genus *Dysidea,* like other species of the same genus in other geographical areas (the only exception in the Mediterranean is *H. coelestis,* which probably needs to be studied further taxonomically, showing metabolites from the sponge *Cacospongia mollior*); *Phyllidia pulitzeri* contains compounds from the sponge *Axinella cannabina; Armina maculata* obtains metabo-

TABLE 1. – Some examples of dietary-derived metabolites in opisthobranch molluscs.

Opisthobranchs	Dietary-derived metabolites	Prey
Philinopsis depicta	aglajne-1, 2 and 3	*Bulla striata*
	haminol-A and B	*Haminoea* spp.
Aplysia depilans	dictyol A, B, C and D	*Dictyota dichotoma*
Hypselodoris villafranca	furanosesquiterpenoids	*Dysidea fragilis*
Doris verrucosa	pyruvic acid oxime	*Hymeniacidon sanguinea*
Discodoris atromaculata	petroformyne 1, 2, 3, 4	*Petrosia ficiformis*
Phyllidia pulitzeri	axisonitrile-1	*Axinella cannabina*
Dendrodoris grandiflora	fasciculatin	*Ircinia fasciculata*
Armina maculata	verecynarmins	*Veretyllum cynomorium*
Flabellina affinis	polyhydroxylated steroids	*Eudendrium* sp.

lites from the pennatulacean octocoral *Veretyllum cynomorium; Cratena peregrina* and species of the genus *Flabellina* have metabolites coming from the hydroid *Eudendrium* sp. (see references in the list).

The most frequently used activity tests are the ichthyotoxicity and the antifeedant (or feeding deterrence) tests. Ichthyotoxicity and feeding deterrence tests have been basically carried out with species that do not live in the same habitat as the opisthobranchs (such as the non-marine fish species *Carassius auratus* and *Gambusia affinis*), and usually following the methodology of COLL *et al.*, (1982) and GUNTHORPE and CAMERON (1987). It is obvious that their ecological validity is questionable, mostly in the feeding deterrence tests. However, as they are simple, quick and easy, both tests are commonly used in chemical laboratories. Sometimes the tests have been done with species from the same habitat as the opisthobranchs (DI MATTEO, 1982; PAWLIK *et al.*, 1988; PAUL *et al.*, 1990). In this area, the fish *Chromis chromis* (CIMINO *et al.*, 1982) and the crab *Carcinus mediterraneus* (FIORITO *et al.*, 1985) have been employed; these species live in contact with the opisthobranchs.

Moreover, from an ecological point of view, we should consider that toxicity or feeding deterrence can affect organisms other than fishes or crabs, for instance echinoderms or other molluscs, and can also exhibit antimicrobial, antiviral, or antifouling activities (on egg masses, for example). But we are still unable to demonstrate their effects in the ecosystem. On the other hand, we can be led to believe that some products have no ecological function and are simply accumulated as waste products, and located in some parts of the body to avoid toxicity for the animal itself. But the fact that the function of many of these chemicals is virtually unknown, does not mean that they do not have a role. In addition, their strategic location in some species indicates some kind of defence purpose (see for instance *Hypselodoris* spp. and *Dendrodoris limbata,* recent work in the list). Some clear examples of allomones are verrucosins of *Doris verrucosa,* some sesquiterpenes of *Dendrodoris* spp. and *Hypselodoris* spp., diterpenes of *Chromodoris* spp., oxytoxins of *Oxynoe olivacea,* etc. Some examples of pheromones are the products from *Haminoea* spp. (for references see the list). However, many others remain to be investigated further.

Cryptic and warning coloration exhibited by opisthobranch molluscs (ROS, 1976) can be related to defensive strategies and chemical products, although more experimental data on the interspecific function of colours are needed (EDMUNDS, 1987). Many described mimicry circles (ROS, 1976) are related to the chemical substances, as in the case of *Hypselodoris* spp. (see references in the list). Relationships between K- and r-strategies can be also found in literature (ROS, 1979; CATTANEO, 1990), but again more data are needed. As a preliminary approach, it seems that *de novo* biosynthetic products are mostly found in K-strategies, and dietary-derived metabolites are found in r-strategies. This preliminary hypothesis would confirm the ideas of ROS *(op. cit.):* the low energy cost used for defence in r-strategy against the high energy cost employed for defence in K-strategy opisthobranchs. It is significant that all the listed species that are able to *de novo* biosynthetize their chemicals belong to the K-strategy groups reported by ROS *(op. cit.):* Sacoglossa and Nudibranchia.

The aims of these kinds of studies are to understand the biological function of chemicals, and when this is known other applications or effects can be found. A clear example is polygodial: its hot taste and strong antifeedant effect are explained according to the chemical structure and biological function (D'ISCHIA *et al.*, 1982; CIMINO *et al.*, 1984, 1985c and d, 1987d, 1988b; CAPRIOLI, *et al.*, 1987). Subsequent studies on polygodial (ÁVILA *et al.*, 1991a) showed that (as hypothesized) only olepupuane is present in the animal: polygodial is only the result of external transformation of olepupuane. Similar examples of this kind of work are studies on prostaglandins from *Tethys fimbria* or cyercenes from *Cyerce cristallina* recently described (see references in the list). In these species some very interesting experiments have been carried out, showing that mechanisms involving secondary metabolites can reach high degrees of complexity. In both examples, the physiological role of metabolites in reproduction and regeneration of cerata have been demonstrated. Co-operation and multidiscipinary research is indispensable in these stu-

dies. In opisthobranch molluscs we should consider that: 1) if we analyze species after dissection, it is possible to localize metabolites in the organism and to discover their function, 2) experiments and tests to check activities should be done with an ecological meaning, showing us a) the role that substances play in the ecosystem, and b) their relationship with the frequent cryptic colorations and aposematic patterns presented (mimicry circles based not only on colours but on chemical products, and the possible existence of batesian mimicry). In that way we will have more data to discuss the biological and ecological function of natural products of opisthobranchs.

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