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Review

Bioactive Compound Synthetic Capacity and Ecological Significance of Marine Bacterial Genus *Pseudoalteromonas*

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Abstract: The genus *Pseudoalteromonas* is a marine group of bacteria belonging to the class *Gammaproteobacteria* that has come to attention in the natural product and microbial ecology science fields in the last decade. Pigmented species of the genus have been shown to produce an array of low and high molecular weight compounds with antimicrobial, anti-fouling, algicidal and various pharmaceutically-relevant activities. Compounds formed include toxic proteins, polyanionic exopolymers, substituted phenolic and pyrolle-containing alkaloids, cyclic peptides and a range of bromine-substituted compounds. Ecologically, *Pseudoalteromonas* appears significant and to date has been shown to influence biofilm formation in various marine econiches; involved in predator-like interactions within the microbial loop; influence settlement, germination and metamorphosis of various invertebrate and algal species; and may also be adopted by marine flora and fauna as defensive agents. Studies have been so far limited to a relatively small subset of strains compared to the known diversity of the genus suggesting that many more discoveries of novel natural products as well as ecological connections these may have in the marine ecosystem remain to be made.

Keywords: *Pseudoalteromonas*, antibiotics, biofilms, anti-fouling, marine bacteria.

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1. Introduction

The genus *Pseudoalteromonas* was described by Gauthier *et al.* [35] and represents a clade of marine bacteria defined on the basis of 16S rRNA gene sequence data. Originally many of the *Pseudoalteromonas* species that are discussed in this review were members of the genus *Alteromonas*

[5, 77] but *Alteromonas* was taxonomically re-organized based on phylogenetic analysis. Since 1995, 22 additional *Pseudoalteromonas* species have been described (details available at http://www.bacterio.cict.fr/p/pseudoalteromonas.html). More recently two *Pseudoalteromonas* species have been moved into the genus *Algicola* [50, 74]. The taxonomy and general features of *Pseudoalteromonas* (*ca*. 2000/2001) are covered in the 2nd edition of *Bergey's Manual of Systematic Bacteriology* [8].

Possessing Gram-negative cell walls, all members of genus *Pseudoalteromonas* require Na^+ ions, form rod-shaped cells, are motile via sheathed polar and/or unsheathed lateral flagella and possess a strictly aerobic, chemoheterotrophic metabolism. This general set of features has coined the common term "alteromonad" that could be potentially used to now describe other marine genera within class *Gammaproteobacteria*. Genus *Pseudoalteromonas* groups within a larger clade of marine taxa, located under the umbrella of order *Alteromonadales* that inhabit all known non-geothermal marine biomes.

One interesting feature of *Pseudoalteromonas* is that the genus can be divided relatively cleanly into pigmented and non-pigmented species clades (Fig. 1) and that pigmentation correlates with their proclivity for natural product formation [22]. The non-pigmented species form a relatively distinct clade typified by phylogenetic shallowness between most member species. Pigmented species show greater sequence divergence and are concentrated within the other 2 major clades making up the genus (Fig. 1). With more than 2000 *Pseudoalteromonas* 16S rRNA gene sequences available on nucleotide sequence databases (e.g. www.ncbi.nlm.nih.gov) the described diversity of the genus still remains largely incomplete.

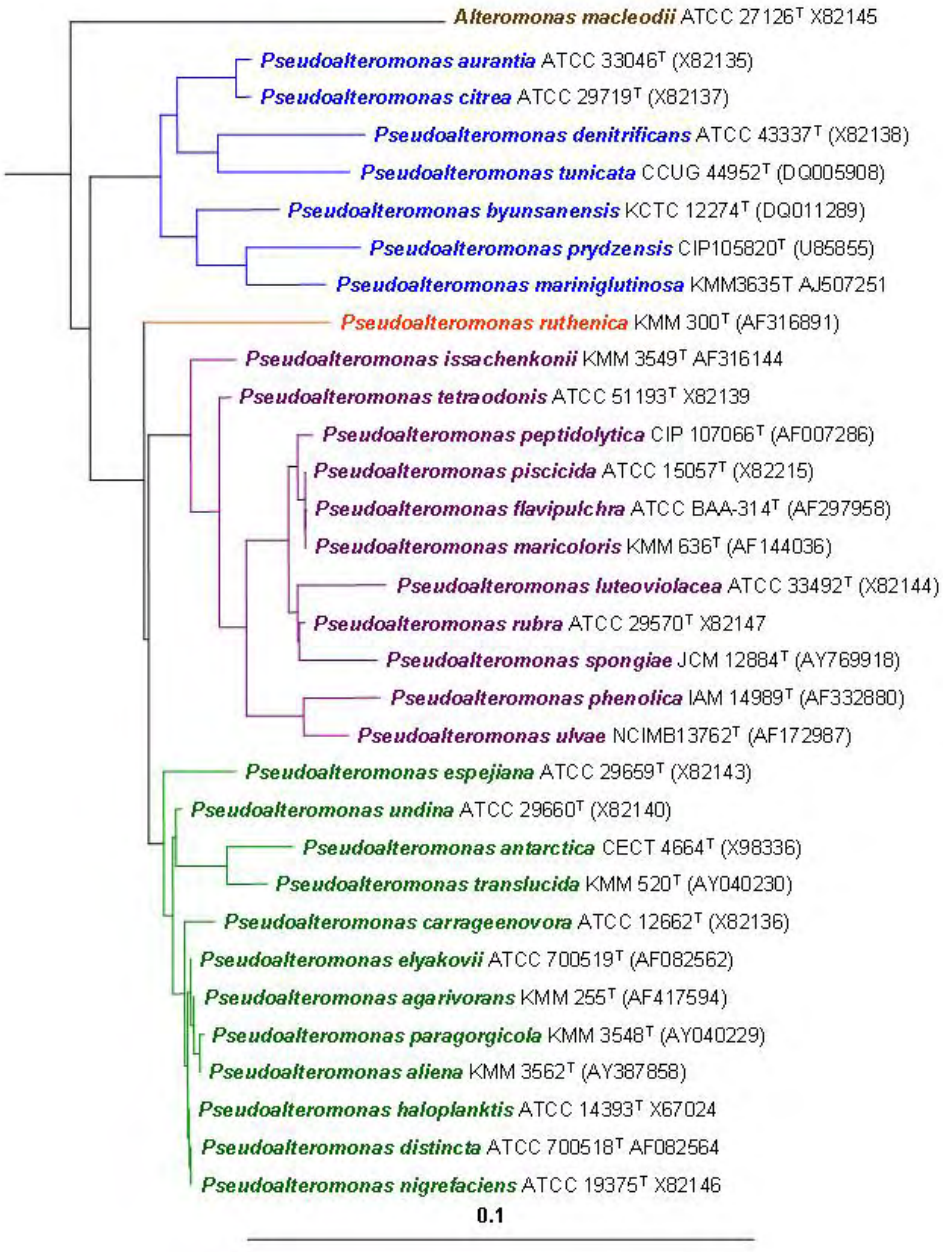
Studies by Holmström *et al.* [43] found deeply pigmented strains within a marine bacterial isolate collection were effective in the inhibition of the settlement of various fouling invertebrates and algae. Based on subsequent analyses some of these isolates lead to the general conclusion that pigmented *Pseudoalteromonas* species possess a broad range of bioactivity associated with the secretion of extracellular compounds, several of which include pigment compounds [44]. This realization provided greater credence to earlier studies of alteromonads that this group of marine bacteria represents a rich source of biologically active substances. Non-pigmented species of *Pseudoalteromonas* do not appear to share the same extensiveness of bioactive compound synthesis and this may reflect their econiche distribution, which is admittedly still poorly defined. Within the limits of existing knowledge non-pigmented clade species tend to possess unusual and diverse enzymatic activities (carrageenases, chitinases, alginases, cold-active enzymes), generally broader environmental tolerance ranges (temperature, water activity and pH) and substantially greater nutritional versatility compared to the pigmented species [8]. The pigmented species also tend to have more exacting growth requirements (some require amino acids) and have peroxidase activity rather than catalase activity.

2. Ecological Significance.

Marine biofilms influence the settlement of a variety of marine invertebrates and algae and may promote cellular metamorphosis. As biofilms can be quite variable in distribution and in species and chemical composition the influence they can have is complex. The activity of marine flora and fauna have been shown to be clearly positively or negatively influenced by experimental monospecific

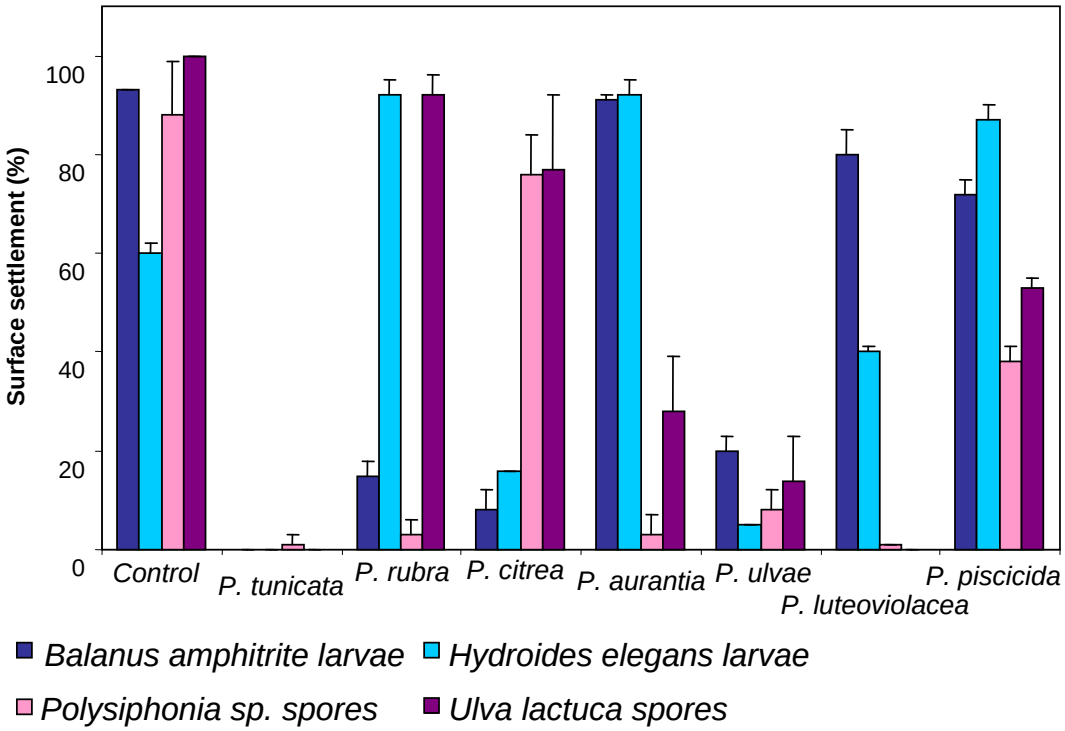
biofilms [17, 82, 98]. This activity is believed to be due mainly to the production of antibiotic compounds as well as stimulatory chemical cues that are so far mostly uncharacterized.

Figure 1. Phylogenetic tree of genus *Pseudoalteromonas* based on 16S rRNA gene sequences (5'-prime region, poisitions 10 to 509 *E. coli* equivalent). Nucleotide distances are based on the maximum likelihood algorithm and the tree clustered using the Neighbor-joining procedure (Phylip v. 3.67; Joe Felsenstein; http://evolution.genetics.washington.edu/phylip.html). Clades within the genus are demarcated in different color type. Species in green are non-pigmented species. Species in blue and purple, as well as *P. ruthenica* are predominantly brightly-pigmented species (see Table 1).



Several known *Pseudoalteromonas* species and likely many other described and undescribed bacterial species can influence the reproductive success of various marine fauna and flora due to the production of natural anti-fouling substances [17] (Table 1). A survey by Holmström *et al.* [42] found that the effectiveness of different *Pseudoalteromonas* species to prevent settlement of fouling invertebrate larvae and algal spores varies considerably (Figure 2).

Figure 2. The inhibition of invertebrate larvae and algal spore settlement by different *Pseudoalteromonas* species. Data adapted from Holmström *et al*. [42].



It was generally observed that algal dwelling species were particularly effective in preventing biofouling suggesting the ability is important for their survival in the marine ecosystem and likely required for effective colonization of various surfaces, especially the surfaces of macroalgal species. *P. luteoviolacea* [34], *P. aurantia* [33]; *P. citrea* [31, 79], *P. tunicata*, and *P. ulvae* [20-22, 45] are of particular interest as the host of compounds these species form are essentially produced to prevent biofilm residents becoming overwhelmed by other colonizing, potentially fouling species [26, 38]. Species resistant to natural antibiotics have an advantage in colonization [83] though presumably due to the array of compounds that may be formed no one species is likely to have such an edge that they always become numerically dominant in a given econiche. The result could be that antibiotic-producing strains and development of synergisms within biofilm communities may actually encourage the formation of multi-species biofilms. This protects the biofilm community from being overgrown by a single species as well as reducing invasion by other species [12]. The complex community formed has the advantage in that there is an inherent increase in the efficiency of nutrient acquisition, enhanced tolerance to toxic compounds and physicochemical stresses, and presumably excellent opportunities for genetic exchange [78]. Ironically, *Pseudoalteromonas* species are highly effective biofilm formers and thus may potentially cause biofouling issues [87], however it is still unknown

whether their presence controls the type and accumulation level of biofouling species beyond specific habitats such as the surface of marine algal species. Quorum-sensing mechanisms may play an important role in the influencing settlement and subsequent biofilm formation [19, 46] though it is unknown to what extent quorum sensing molecules influence antibiotic production.

Table 1. Bioactive compound production and associated activities by described *Pseudoalteromonas* species.

Species	Pigmented [a]	Source	Bioactive compounds[b]	Inhibitory activities [other activities][b]
P. aliena	+ (melanin)	seawater	Unknown compound(s) formed	Anti-tumorigenic activity - Ehrlich ascites carcinoma cell line inhibited[c]
P. agarivorans	-	seawater, ascidians	-[d]	-[d] [degrades algal polysaccharides]
P. antarctica	-	seawater, sea-ice, muddy soils, sediment	-	None observed[e,f] [novel polysaccharides, cold-active enzymes]
P. atlantica	-	seawater, marine alga	-	May cause opportunistic disease in crabs [strong degrader of algal polysaccharides]
P. aurantia	+ (yellow)	surface of *Ulva lactuca*, seawater	Unknown compound(s) formed	Antimicrobial activity; inhibits settlement of invertebrate larvae
P. byunsanensis	-	tidal flat sediment	-	-
P. carrageenovora	-	seawater, marine alga		None observed[e] [strong degrader of algal polysaccharides]
P. citrea	+ (yellow, melanin)	seawater, mussels, ascidians, sponges	Unknown compound(s) formed	Inhibits settlement of invertebrate larvae; cytotoxic against sea urchin [algal polysaccharide degradation]
P. denitrificans	+ (red)	seawater	high molecular weight polyanionic substance; cycloprodigiosin HCl	Anti-tumorigenic activity; inhibits T-cell/lymphocyte proliferation; anti-malarial activity; induces settlement of sea urchin *Heliocidaris erythrogramma*[g]
P. distincta	± (melanin)	sponge	-	-
P. elyakovii	-	mussels, marine alga	-	None observed[e,f]
P. espejiana	-	seawater	-	None observed[e,f]
P. flavipulchra	+ (orange)	seawater	-	-
P. haloplanktis	-	seawater	novel diketopiperazines	- [Probiotic benefits to shellfish; cold-active enzymes]
P. issachenkonii	-	marine alga	isatin; unknown reddish-brown compound	Anti-fungal activity; hemolytic
P. luteoviolacea	+ (purple, yellow)	seawater, marine alga	toxic antimicrobial protein; brominated pyrrole-containing compounds, 4-benzaldehyde; *n*-propyl-4-hydroxybenzoate	Antimicrobial activity; inhibits algal spore settlement; cytotoxic against sea urchin *Strongylocentrotus intermedius*; induces settlement of sea urchin *Heliocidaris erythrogramma*[g]

Table 1. Cont.

P. maricoloris	+ (yellow)	sponges	bromo-alterochromides A and B	Antibacterial activity; cytotoxicity against sea urchins
P. marina	-	tidal flat sediment	-	-
P. mariniglutinosa	-	diatoms	-	-
P. nigrifaciens	± (melanin)	seawater, salted foods, mussels	-	-
P. paragorgicola	-	sponge	-	-
P. peptidolytica	+(yellow)	seawater	unknown compounds	Antimicrobial activity, hemolytic[e]
P. phenolica	+ (brown)	seawater	3,3',5,5'-tetra-bromo-2,2-biphenyldiol	Antimicrobial activity
P. piscicida (and related bacteria)	+ (yellow)	estuarine waters, fish samples	toxic protein; possible yellow cyclic/acyclic brominated depsipeptide compounds; unknown anti-algal compound(s)	Antibacterial; algicidal activity; possible cytotoxicity [opportunistic fish pathogen; thrombolytic enzymes]
P. rubra	+ (red)	seawater	high molecular weight polyanionic substance; cycloprodigiosin HCl; rubrenoic acids	Antimicrobial activity; anti-tumorigenic activity; inhibits T-cell/lymphocyte proliferation; anti-malarial; bronchodilatatoric[e,f]
P. ruthenica	+(pale orange)	shellfish	unknown compounds	Antimicrobial activity
P. spongiae	+ (pale orange)	sponge	-	Strongly induces settlement of *Hydroides elegans*
P. tetraodonis	-	puffer fish	tetrodotoxin	Neurotoxic effects[e,f]
P. translucida	-	seawater	-	-
P. tunicata	+ (green, purple, yellow)	marine alga, tunicates	unknown purple pigment; tambjamine-like alkaloid YP1; toxic protein AlpP; other unknown sunstances	Anti-fungal, anti-algal, antimicrobial, inhibits settlement of invertebrate larvae and algal spores; inhibits protists
P. ulvae	+ (purple)	marine alga	unknown substances	Inhibits invertebrate larval settlement and algal spore germination and settlement
P. undina	-	seawater, fish	-	hemolytic; [probiotic benefits; possible opportunistic fish pathogen]

[a] Data is obtained from species description papers listed at http://www.bacterio.cict.fr/p/pseudoalteromonas.html.

[b] Data on natural compounds with known structural data and associated activity are detailed in sections 3 and 4.

[c] Pigments not formed under standard growth conditions. Melanin production is stimulated when grown on L-tyrosine and/or 3,4-dihydroxyl-L-phenylalanine. Butanol extracts inhibited an Ehrlich's ascites carcinoma cell line [51].

[d] No published natural product or bioassay data for these species is available.

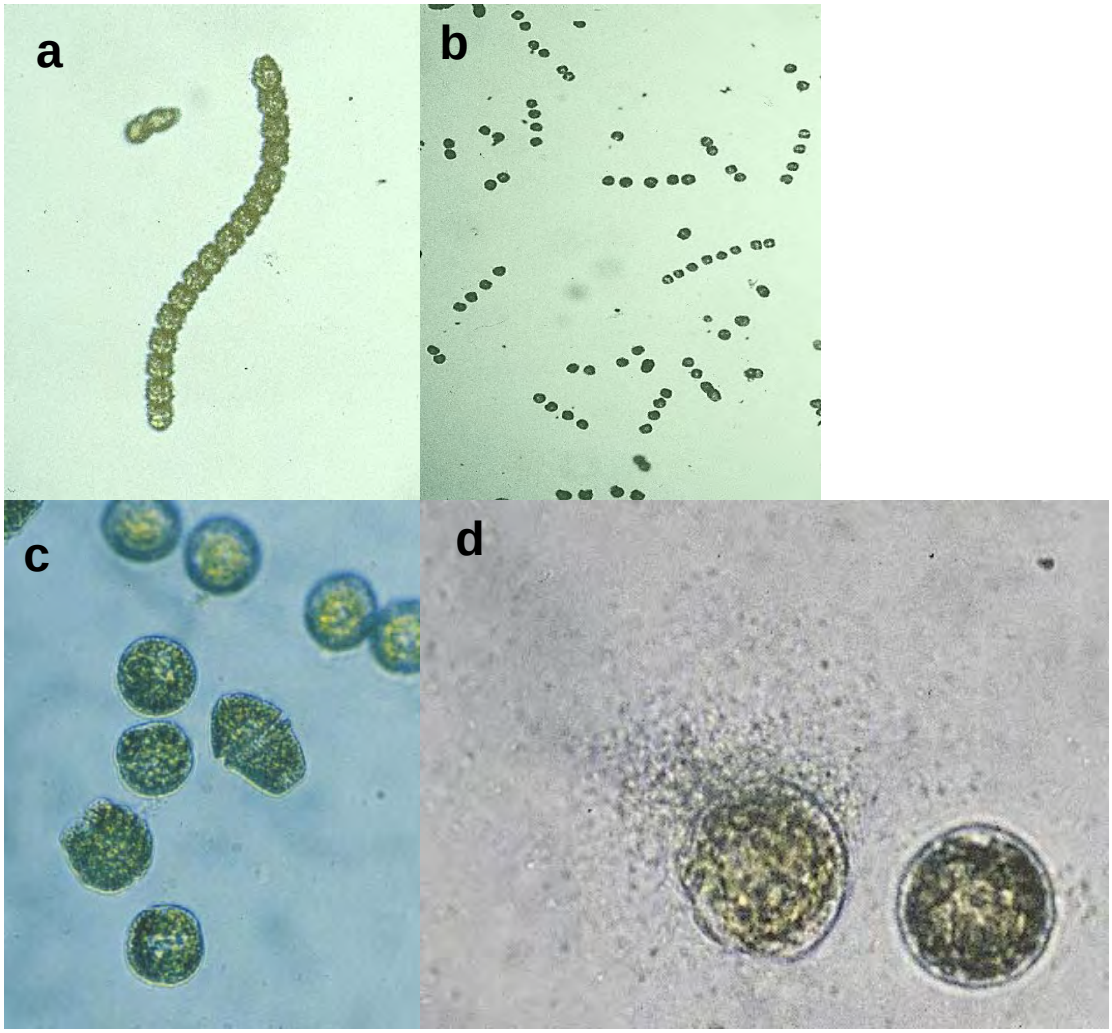
[e] Ethyl acetate and butanol extracts negative for antimicrobial and haemolytic activity [54].

[f] Ethyl acetate extracts negative for cytotoxicity against sea urchin *Stronglyocentrotus intermedius* [54].

[g] Data from Huggett *et al.* [48].

Pseudoalteromonas species have been found to inhibit the settlement, germination, growth or even directly lyse the cells of various algal species. Thus the interactions *Pseudoalteromonas* strains are involved is intricate dictated by the type of ecosystem involved (planktonic, benthic, surficial etc.), physiological state populations of the species involved, and prevailing environmental chemical parameters. At this point in time specific aspects of these ecological networks remain largely unexplored. To make the ecological connections even more manifestly complex strains of *Pseudoalteromonas* have also been shown to have promotive affects on various marine eukaryotes in regards to their potential reproductive success.

Figure 3. Anti-algal activity of *Pseudoalteromonas* species strain Y on the dinoflagellate *Gymnodinium catenatum.* a) Typical chain form of *G. catenatum* (time 0-10 minutes). b) Cell chains disassemble into individual cells (T=20 minutes); c) Cells become rounded (T=45 minutes; d) Cell lysis and leakage with strain Y swarming to a lysis cell (T=3 hours). Data and figures adapted from [92, 93].



An example of an inhibitory-oriented interaction involves unidentified strains of *Pseudoalteromonas* [18, 62] that were found to inhibit the growth but not kill various diatom species due to production of antibiotic compounds. One of these compounds was identified as 2-heptyl-4-

quinolinol (Fig 6I) [62] that have been found to possess antibacterial activity [101]. Another strain, *Pseudoalteromonas* sp. 4 produced unknown substances that impeded the motility and surface attachment of a *Navicula* sp. and *Amphora coffeaeformis.* These diatoms eventually underwent lysis. This ability could be blocked by enhancing lectin formation by the diatoms leading to stronger biofilm attachment [99]. A further different example involves strain Y, closely related to *Pseudoalteromonas piscicida*, which produces unidentified brominated antibiotic compounds as well as an unknown low molecular weight compound that can completely lyse algal cells within a matter of hours [64, 92, 93]. This more "aggressive" activity was found to be pronounced on bloom-forming toxin-producing dinoflagellates of the genera *Gymnodinium*, *Chatonella* and *Heterosigma* species, however only ecdysis was observed for *Alexandrium* species while diatom and other algal species tested were effectively immune. The progress of this lytic effect on *Gymnodinium catenatum* is shown in Figure 3. It was also observed that cells were attracted in a swarm to lysed cells providing the concept that the compound production is used as a means to generate nutrients in a predatory-like manner. Subsequently it was determined that production of the unknown algicidal factor was triggered by an autoinducer quorum sensing system, possibly an AI-2-type peptide [93] and that it is likely that algicidal activity is maximal during the peak of algal blooms and may thus contribute to bloom dissolution.

Pseudoalteromonas clearly also positively interacts with higher eukaryotes inducing invertebrate larval settlement and subsequent metamorphosis. *P. espejiana* was observed to induce the settlement and metamorphosis of the hydrozoan *Hydractinia echinata* [59] possibly due to induction of caspases [88], suggesting *Pseudoalteromonas* strains may have apoptosis-inducing effects in some marine eukaryotes. *Pseudoalteromonas* sp. A3, interestingly closely related to *P. piscicida*, isolated from the crustose coralline algae *Hydrolithon onkodes* clearly encouraged coral larvae settlement and subsequently induced metamorphosis in the planula of the coral *Acropora* [75]. The presumed chemical cue for this induction has not yet been discovered, however methanolic extracts of A3 cultures provided induction that was highly variable. A further example includes an extensive survey of marine bacterial isolates from coralline algae and larvae, from which 12 of 17 *Pseudoalteromonas* strains were found to be effective in inducing the larval settlement of the sea urchin *Heliocidaris erythrogramma*. It was also observed that the larvae metamorphosed in higher numbers on biofilms consisting of *P. luteoviolacea* [48] a species known to produce several antibiotic and bioactive compounds. Huang *et al.* [47] demonstrated that biofilms strongly promoted the settlement of *Hydroides elegans* larvae suggesting that when in the biofilm state chemical cues are actively formed.
It is important to note that biofilm communities are dynamic complex entities. The direct detection of antibiotic compounds formed from artificial laboratory biofilms has been challenging [40] possibly due to lack of replicability of natural biofilms as well as due to the variable abundance of antibiotic-producing taxa.

These examples suggest that chemical substance production may help various *Pseudoalteromonas* species compete in quite different situations. The advantages derived could include increased access to space for growth or for nutrient access and potentially can occur in marine biofilms or planktonically. It is not clear how significant or prevalent these interactions are for planktonic and benthic sediment associated cells or for cells ensconced in sinking marine aggregates. Mechanistically the processes involved are also poorly understood and how these activities contribute to larger networks of

ecological interactions. Thus the questions that involve *Pseudoalteromonas* are manifold. Keeping with the theme of antibiotics, a popular subject in microbiology, the significance of cell-to-cell proximity, dilution rate and inherent antibiotic resistance within natural settings in regards to natural antibiotics are still open questions. In marine biology a greater interest may exist on what are the different "broadcasted" chemical cues produced by bacteria, including *Pseudoalteromonas* that may affect the development or growth of eukaryotes as well as other prokaryotes. Assuming chemical cues can be identified we still need know what they do exactly, why and how. The contribution of many different factors suggests that understanding the ecological ramifications and impact of natural bioactive compounds can only be approached at first by specific, controlled experiments focusing on "model" species, a necessary simplification that allows important specific ecologically to better conceived and tested. One such model species that has appeared within the last few years is *P. tunicata*, a species that possesses an unusually extensive capacity for inhibiting other types of microorganisms and larger eukaryotes and is the focus of the Prof. Staffan Kjelleberg research team at the University of New South Wales, Sydney, Australia.

3. *P. tunicata* as a model to study the mechanisms and ecology of natural antibiotic production, anti-fouling activity and biofilm formation.

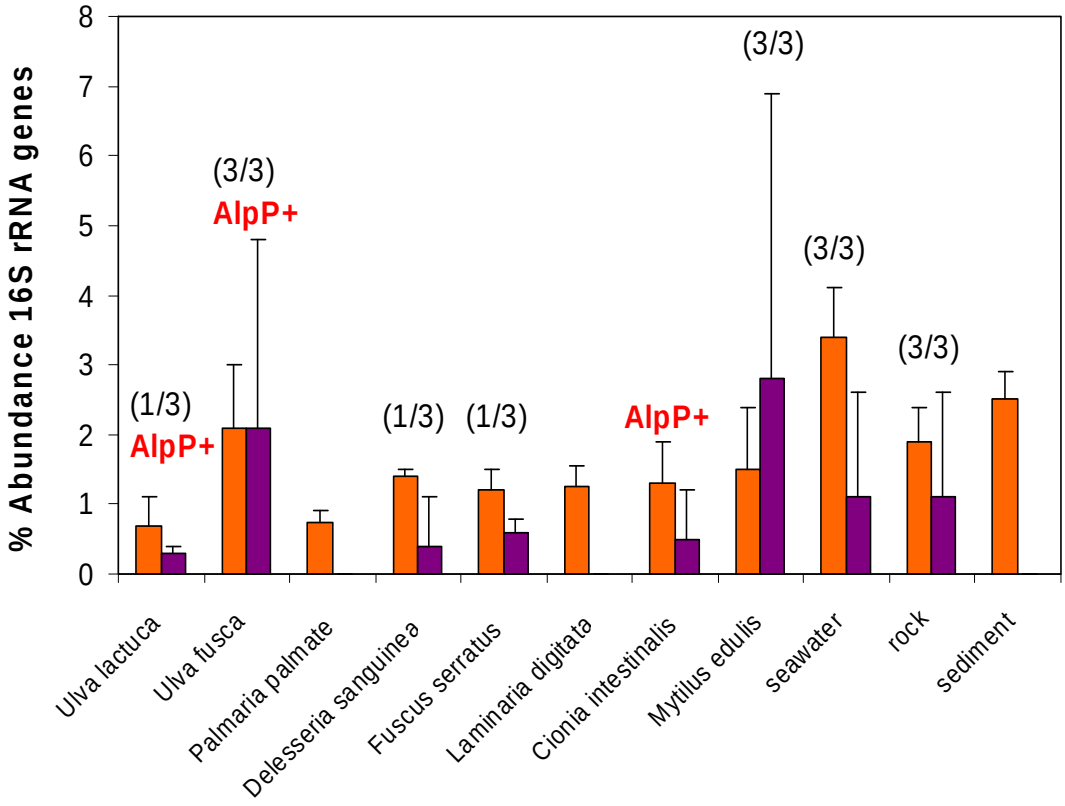
P. tunicata possesses the highest and broadest range of anti-fouling activities observed to date and was first isolated from a tunicate off the coast of Sweden [45] and subsequently found to dwell on a number of marine species, especially macroalgae [20, 44]. Transposon mutagenesis analysis demonstrated the pigment production by the species is linked to this activity [22, 23] and includes both purple and yellow pigments that give *P. tunicata* a distinctly dark green-color. The purple pigments were found to prevent the settlement of invertebrate larvae (*Balanus amphrtite, Hydroides elegans*) and algal spores (*Ulva lactuca*, *Polysiphonia* sp.) (Figure 2) but remains unidentified. The species *P. ulvae*, isolated from the surface of the seaweed *Ulva lactuca*, was found to also inhibit the settlement of invertebrate larvae (*Balanus amphritite*) and inhibit algal spore germination and settlement [20, 21]. The purple pigment formed by *P. ulvae* may be chemically similar to the compound(s) found in *P. tunicata* and other *Pseudoalteromonas* species [22].

The anti-fouling ability of *P. tunicata* is linked to its ability to produce a range of inhibitory substances (more details below) including a toxic antibiotic protein (AlpP) [52]; a heat labile anti-algal substance [21]; violet-colored polar compound(s) of <500 Da [43]; an antifungal yellow pigment compound [25] as well as small molecules active against protists and diatoms (unpublished data). WmpR, similar to the *Vibrio cholerae* cholera toxin regulator ToxR, was found to act as a response regulator activating several genes in *P. tunicata* including pigment and antifouling compound production, biofilm formation, type IV pili, some ubiquinone and amino acid synthetic genes, a putative Fe^{3+} complex TonB-type transporter and also a non-ribosomal peptide synthetase that possibly is involved in Fe^{3+} siderophore synthesis. The wild type strain survives iron starvation better than a ΔWmpR mutant suggesting that the tendency of *P. tunicata* to colonize surfaces and produce antifoulants is controlled by nutrient related responses, perhaps acquisition of trace iron [23, 96]. *P. tunicata* appeared to be most effective in colonization when it had access to an exogenous carbon source associated with the colonization surface e.g. cellobiose derived from degradation of the

cellulose surface polymer of the macroalgal species [83]. This may suggest the types and levels of nutrient available for growth may also drive colonization.

Population estimates of antifouling species *P. tunicata* and *P. ulvae*, able to form toxic protein AlpP, has been made by using real-time PCR targeting *Pseudoalteromonas*-specific and *P.tunicata/P.ulvae*-specific 16S rRNA genes as well as detection of the gene coding AlpP [94]. It was found that from various samples collected off the Danish coast that *Pseudoalteromonas* are abundant, especially in seawater (Figure 4). *P. tunicata* and *P. ulvae*, however prefer colonization of various cellulose-producing algal species as suggested by the specific abundance of anti-fouling *Pseudoalteromonas* spp, positive detection of the *alpP* gene (Fig. 4) and PCR-DGGE fingerprinting. Almost all of the antifouling species found were related to *P. tunicata* and *P. ulvae* but these only made up about 1% of the total *Pseudoalteromonas* abundance. This may suggest that other species await isolation that could also have anti-fouling roles on the hosts sampled or the specific populations change over time as the biofilm matures. Based on the compiled data shown in Figure 2 [42] the variation in settlement inhibition assays is highly species-specific (and possibly strain-specific) and that marine macrophyta and marine fauna may play host to their own specific anti-fouling microorganisms.

Figure 4. Abundance of *Pseudoalteromonas* (compared to total bacteria; orange bars) and abundance of anti-fouling species *P. tunicata* and *P. ulvae* (compared to total *Pseudoalteromonas*; purple bars) on various marine alga, invertebrates, rocks and in sediment. Error bars are standard deviations of results from 3 separate samples. Numbers in parentheses indicate the number of samples showing the presence of the biofouling species in DGGE analyses. The presence of toxic protein AlpP (as determined by positive PCR results for the *alpP* gene) is indicated in red type. Data adapted from Skovhus *et al*. [94].



4. Natural product compound production by *Pseudoalteromonas* spp.

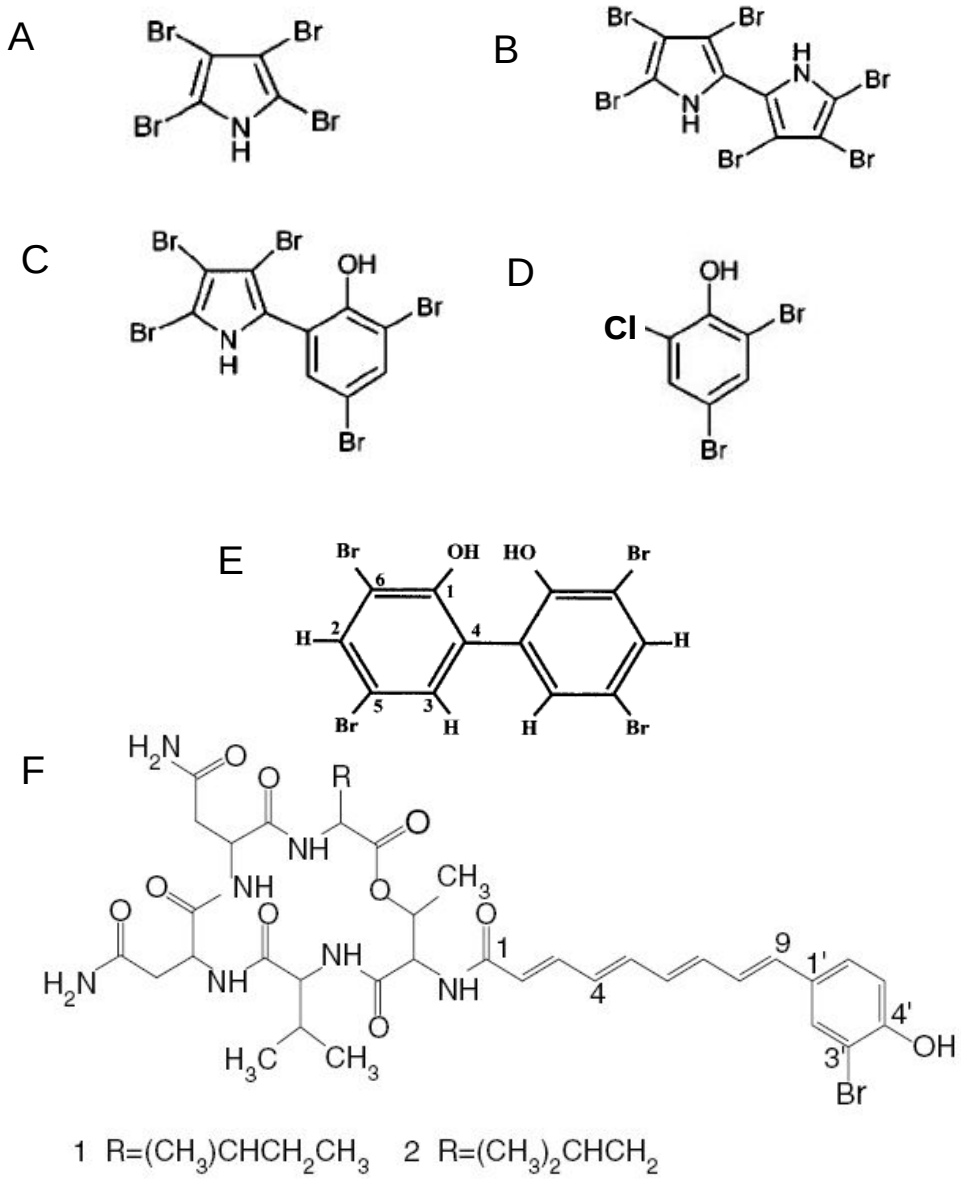
Antibiotic substances linked to the genus *Pseudoalteromonas* go back to the very early days of marine natural product discovery. Over the years several *Pseudoalteromonas* strains that have been investigated in this regard have been misidentified or misclassified as *Pseudomonas*, *Chromobacterium*, *Alteromonas* etc. With the current rate of bacterial genus and species descriptions from marine samples, it is difficult if not impossible to be certain of genus identities (let alone species) from the limited taxonomic analyses applied in the times prior to routine sequence based bacterial identification. The information below is based on strains that on the basis of existing data can be attributed at a high level of confidence to the genus *Pseudoalteromonas*.

4.1. Low molecular weight substances.

Early discoveries of marine-derived antibiotics included the identification of brominated pyrroles from purple-pigmented alteromonads. 2,3,4-tribromo-5(1'-hydroxy-2',4'-dibromophenyl)pyrrole was identified from a strain isolated from a *Thalassia* sp. [65]. Several low weight antibacterial substances were obtained from *P. luteoviolacea* misclassified initially as *Chromobacterium marinum* [32]. These included 2,3,4,5-tetrabromopyrrole (Figure 5A), 2,2',3,3',4,4'-hexabromobipyrrole (Figure 5B), 2,3,4-tribromo-5(2'-hydroxy-3',5'-dibromophenyl)pyrrole (also called pentabromopseudilin) (Figure 5C), 2,4-dibromo-6-chlorophenol (Figure 5D), 4-hydroxybenzaldehyde, and *n*-propyl-4-hydroxybenzoate [2, 11, 24, 32, 34, 37, 85, 86]. One or more of these substances also seem to also have activity against protists [55]. The seawater species *P. phenolica* was also found to form a brominated biphenyl compound, 3,3',5,5'-tetrabromo-2,2'-diphenyldiol (Figure 5E) that was inhibitory to methicillin resistant *Staphylococcus aureus* strains [49].

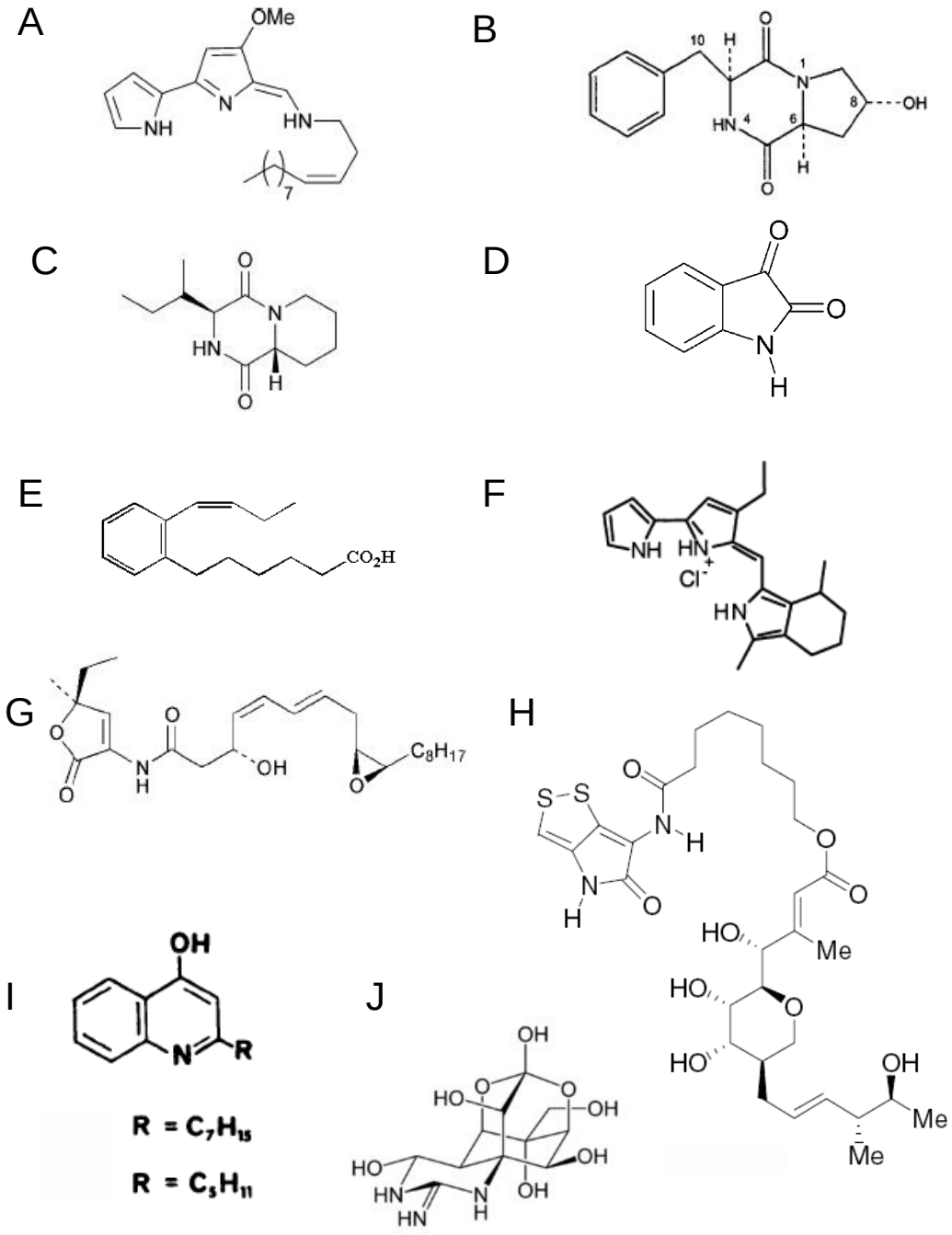
The yellow pigment of *P. tunicata* has anti-fungal activity [22] and was identified as a tambjamine-like alkaloid, designated YP1 [25] (Figure 6A). Tambjamines are 4-methoxypyrrole-containing bioactive compounds previously isolated from marine invertebrates and possess antimicrobial, anti-tumorigenic, immunosuppressive, anti-proliferation and ichthyodeterrent activities [61] and are likely produced as natural defensive compounds against predators. Most evidence points to bacteria, colonizing the surface of higher organisms, as the source of these compounds [58]. Indeed, the biosynthetic pathway for YP1 was elucidated in *P. tunicata* by Burke *et al*. [10] and is coded by a cluster of 19 genes (*tamA* to *tamS*) that code proteins with homology to prodigiosin biosynthetic genes in various other bacteria [100], including the formation of a bipyrrole precursor, 4-methoxybipyrrole-5-carbaldehyde (MPC) from proline, malonyl-CoA and serine. YP1 is formed by condensation of MPC with dodec-3-en-1-amine [10]. A related compound to YP1 acts as an ionophore [97]. The bright red pigments of *P. denitrificans* and *P. rubra* identified as cycloprodigiosin HCl (Figure 6F) [36, 56] also acts as an ionophore blocking proton/chloride ion symporters but have been shown to generally uncouple proton translocation [67]. It has significant potential pharmaceutical impact able to suppress immunoproliferation [68], has anti-malarial activity [57] and is able to induce apoptosis in several cancer cell lines [13, 80]. In synergy with other drugs cycloprodigiosin may have an anti-tumorigenic application.

Figure 5. Brominated compounds formed by *Pseudoalteromonas* species. See text for more information.



Substituted phenylalkenoic acids referred to as rubrenoic acids (Figure 6E) have also been purified from *P. rubra* and shown to have bronchodilatatoric activity [41]. The species *P. tetraodonis* (as well as a number of other bacterial species), isolated from the skin slime of the puffer fish *Fugu poecilonorus*, was shown to form the notorious tetrodotoxin (Figure 6J) [27, 91], which is an exceptionally potent blocker of voltage-gated, Na^+ ion membrane channels. Production of tetrodotoxin by *P. tetraodonis* was dramatically stimulated under phosphate-limiting growth conditions [28]. Korormycin (Figure 6G), produced by an unidentified *Pseudoalteromonas* sp., is a heptylated hydroxyquinonolone that has antibiotic activity against various marine bacteria, especially *Vibrio* spp. It was found to strongly inhibit the respiratory chain-linked Na^+-ion translocating NADH-quinone reductase of *Vibrio alginolyticus* [103].

Figure 6. Non-halogenated low molecular weight compounds produced by *Pseudoalteromonas* species. See text for details.



Butanol extracts of the algal associated species *P. issachenkonii* cultures were found to inhibit *Candida albicans* and cause hemolysis. Analysis of ethyl acetate extracts revealed that isatin (indole-2,3-dione) (Figure 6D) was responsible for the anti-fungal activity. A red-brown haemolytic pigment of 269 Da and corresponding to $C_9H_7N_3OS_3$ was also discovered and still awaits complete structural analysis [54]. A possibly misidentified *Pseudoalteromonas* species designated *Alteromonas* sp. P7, isolated from the larva of *Penaeus monodon* was found to be vibriostatic with the antibacterial substance recovered in ethyl acetate but not the culture supernatant suggesting the compound may also be a substituted aromatic compound [1]. A potentially misclassified pigmented *Pseudoalteromonas*-

like species called "*Alteromonas rava*" was found to form a substituted 6-amino-4*H*-[1,2]dithiolo[4,3-*b*]pyrrol-5-one called thiomarinol A (Figure 6H). Various thiomarinol derivatives have been also synthesized that exhibit potent antibacterial activity [89, 90].

The yellow-pigmented species *P. piscicida* has been described as being able to produce a neuromuscular toxin able to kill a variety of fish and crab species [7, 39, 72], however no recent studies have re-examined or confirmed this property and the toxin compound has never been detected. This may suggest *P. piscicida* is rarely an opportunistic pathogen. Strains were also described as being able to inhibit the growth of yeast [9]. *P. maricaloris*, a close relative of *P. piscicida* isolated from the Coral Sea sponge *Fascaplysinopsis reticulata*, forms yellow colored dibromo- and bromo-alterochomides (Figure 5F) that possess antimicrobial activity and as well as cytotoxicity against the larvae of a sea urchin [95]. The algicidal strain Y, also closely related to *P. piscicida*, forms broad spectrum antimicrobial yellow brominated substances that LC-MS analysis revealed to comprise 12 different but likely structurally similar compounds. The molecular weights of the most abundant components ranged from 830-954 [92]. NMR spectral analysis revealed the presence of bromine, aromatic rings, hydroxyl and carbonyl groups. These still so far unidentified substances may also represent other cyclic or acyclic depsipeptide brominated compounds and may be relevant to the observation of other low molecular weight peptide like substances potentially contributing to anti-fouling activity [104]. A variety of diketopiperazines (DKP) are produced by an Antarctic *Pseudoalteromonas haloplanktis* isolate [73] including a novel compound, cyclo-(D-pipecolinyl-*L*-isoleucine) (Figure 6C). This novel DKP was inactive in a free radical scavenging assay using 1,1-diphenyl-2-picrylhydrazyl. Another novel DKP, cyclo-(*L*-phenylalanyl-4*R*-hydroxyl-*L*-proline) (Figure 6B) is produced by *P. luteoviolacea* [53] that exhibited antibacterial activity. The continued examination of peptide like pigment and non-pigment substances from *Pseudoalteromonas* appears to be necessary as these compounds seem to have a potentially important impact in biological interactions.

4.2 High molecular weight substances.

Several *Pseudoalteromonas* species have been found to secrete proteins and other soluble high molecular weight substances with antibacterial activities that are also autotoxic in nature [3]. This included a 100 kDA protein produced by *P. luteoviolacea* [34], which was likely also observed in the study of Kamei *et al*. [55]. The synthesis of this protein appeared to be induced during late exponential to stationary growth [71]. *P. rubra* was found to form a strongly anthrone-reactive polyanionic substance, possibly a glycoprotein or polysaccharide, which had antibacterial activity, especially to species that did not naturally possess catalase activity. Subsequently it was found that growth inhibition by the antibiotic was due to induction of oxidative stress in target cells through increased O_2 uptake and accumulation of hydrogen peroxide [29, 30]. An alteromonad, designated NCIMB 2144, was found to produce an autotoxic, antibacterial 90 kDA thermolabile glycoprotein [4] that could be analogous to that found in *P. rubra*. *P. tunicata* strain D2 secretes an autotoxic 190 kDa dimeric protein referred to as AlpP. This protein was found to inhibit a wide range of marine and medically significant bacteria [52] but is particularly potent against strain D2 itself (MIC 4 μg mL^{-1}). However, as cells progress into the stationary growth phase they become increasingly resistant. The autoxicity of

AlpP appears to provide a dispersal mechanism to biofilm dwelling *P. tunicata*, working through a process akin to programmed cell death [6]. The AlpP-autolysis of cells within biofilm substructures seems to provide nutrients for a subpopulation of cells resistant to AlpP with the lysis causing sections of the biofilm to also detach. Survivor cells are actively motile and presumably are dispersed in the water flow and thus can recolonize new surfaces [69, 70]. Observations in other bacteria suggest dispersal mechanisms analogous to this could be relatively common amongst biofilm forming species [6]. An isolate related to *P. piscicida*, designated X153 has been proposed as an effective probiont, protecting commercial shellfish species from pathogenic *Vibrio* species. X153 was shown to produce a, unstable tetrameric 280 kDa vibriostatic protein that also appeared to have broad spectrum inhibitory activity against marine bacteria [63]. *P. haloplanktis* and *P. undina* strains have also been found to provide probiotic benefits [66, 84] though it is unknown if antibiotic factors are involved.

Some species of *Pseudoalteromonas* have been rarely implicated as opportunistic pathogens of marine animals including fish and crustacea [14, 76, 81]. This pathogenicity may relate to lipopolysaccharide and other heat labile factors [15] and other virulence determinants such as hemolysins [54] and thrombolysins [16]. The structure of O-specific polysaccharides has been determined for a number of *Pseudoalteromonas* species, which are notable in being acidic and containing a variety of substituted sugar and non-sugar subunits [60]. It is unknown if these substances have antibiotic or cytotoxic properties in the marine environment.

5. Concluding Remarks

Pseudoalteromonas though it appears to be only one of many marine bacterial genera (either cultured or uncultured) clearly has been shown to possess ecologically- and pharmaceutically-relevant features that are both unusual and intriguing. Greater understanding of the activities of this genus in the marine ecosystem would represent a boon to microbial and marine ecology. More knowledge of the biologically active chemicals formed by *Pseudoalteromonas* species would also be potentially pharmacologically beneficial. Such research could be performed from a marine biology point of view in order determine the relationships of *Pseudoalteromonas* to the reproductive success of many invertebrates and algal species. Detection and identification of new chemical cues could be valuable in understanding the interactive ecology of marine fauna and their associated microbiota. It could also be expanded to conservation-oriented dimensions. Negri and colleagues [75] proposed there is a possibility that broadcast chemical producing bacteria like *Pseudoalteromonas* sp. A3 could be used as a means to re-seed reefs with coral species owing to its positive effects on coral larvae settlement and metamorphosis. It is unknown if any of these undiscovered compounds would have pharmaceutical benefit too or would have other applications. In that respect several broad spectrum antibiotic compounds have been detected from *Pseudoalteromonas* spp. including pentabromopseudilin, korormycin, thiomarinol A, bromo-alterochromides A and B, tambjamine YP1 etc. Various strains also form compounds with intriguing pharmaceutical properties such as the red pigment cycloprodigiosine HCl. Since these substances have been derived from only a small subset of strains the potential pool of natural product diversity possessed by genus *Pseudoalteromonas* is likely mostly unrealized.

Proteases from various strains of *Pseudoalteromonas*, in particular from a strain of *P. issachenkonii* were recently found to be effective in reducing biofouling by the bryozoan *Bugula*

neritina [19]. The innovative practical application of small and large antibiotic compounds as well as proteinaceous enzymatic substances to combat marine biofouling is progressing through the use of paints and gel-encapsulation [19, 102]. Thus the extensive enzymatic ability of various *Pseudoalteromonas* (as suggested for some species in Table 1) is also worth noting as this generally unexplored facet can be potentially useful in a practical sense to combat biofouling as well as an ecologically relevant feature.

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