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Marine unsaturated fatty acids: structures, bioactivities, biosynthesis and benefits

 Yingfang Lu,^a Yinning Chen,^b Yulin Wu,^a Huili Hao,^a Wenjing Liang,^c Jun Liu^{*d} and Riming Huang  ^{*a}

Unsaturated fatty acids (UFAs) are an important category of monounsaturated and polyunsaturated fatty acids with nutritional properties. These secondary metabolites have been obtained from multitudinous natural resources, including marine organisms. Because of the increasing numerous biological importance of these marine derived molecules, this review covers 147 marine originated UFAs reported from 1978 to 2018. The review will focus on the structural characterizations, biological properties, proposed biosynthetic processes, and healthy benefits mediated by gut microbiota of these marine naturally originated UFAs.

1 Introduction

Fatty acids other than saturated fatty acids (fatty acids that do not contain double bonds are called saturated fatty acids, and all animal oils, except fish oils, contain saturated fatty acids) are unsaturated fatty acids. Unsaturated fatty acids (UFAs) consist of a long-chain hydrocarbon with the presence of at least one double covalent bond and ending in a carboxyl group ($-COOH$), and are distinguished into monounsaturated fatty acids and polyunsaturated fatty acids, both of which have numerous beneficial properties to human health.^{1,2} These secondary metabolites have previously been obtained from a variety of natural resources, including marine fish oils that are a good natural source of these UFAs.^{3,4} In previous decades, marine derived UFAs have attracted a great deal of interest because of their structural diversity and potential biological and nutritional functions.⁵ In particular, research interest in omega-3 fatty acids,⁶ eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from marine organisms, has dramatically increased as they are excellent sources of nutrients. These UFAs also can be described as *cis* fatty acids *versus* *trans* fatty acids, which is a description of the geometry of their double bonds. These characteristics in UFAs not only enable them to show a broad

range of biological activities, but also allow the development of the nutrient-like physicochemical properties. However, most of marine derived UFAs belong to a relatively unexplored category that may hold a great promise for the potential nutritional application in the future. The structures and potential nutritional applications of UFAs, particularly these with the interesting biological activities have previously been reviewed,^{7,8} but there is still lack of a comprehensive review about marine derived UFAs. Thus, this review aims to summarize 147 marine organisms-derived UFAs published from 1978 to 2018. The review will focus on the structural characterizations, biological properties, proposed biosynthetic processes, and benefits mediated by gut microbiota of these marine UFAs. In addition, the origin of the isolation of these UFAs is also taxonomically presented.

2 Monounsaturated fatty acids

Up to date, there are 14 of total monounsaturated fatty acids obtained from marine organisms, linear and branched monounsaturated fatty acids **1–14** (Table 1 and Fig. 1).

2.1 Linear monounsaturated fatty acids

2.1.1 Sponges. Only one linear monounsaturated fatty acid, namely, 10-tricosenoic acid **1** was isolated from *Calyx podatypa*.⁹

2.2 Branched monounsaturated fatty acids

2.2.1 Sea cucumber. The Caribbean sea cucumber *Holothuria mexicana* contained (6Z)-7-methyloctadec-6-enoic acid **2** that was found in the phospholipid fraction.¹⁰

2.2.2 Sponges. Two long 2-methyl substituted fatty acids **3** and **4** were isolated as methyl esters from *Halichondria panicea* (Sea of Japan, Russia).¹¹ 7-Methyl-9-oxo-dec-7-enoic acid **5** was isolated from an *Ircinia* sp. (Red Sea).¹²

^aGuangdong Provincial Key Laboratory of Food Quality and Safety, College of Food Science, South China Agricultural University, Guangzhou 510642, China. E-mail: luyingfang@stu.scau.edu.cn; DanielWu@stu.scau.edu.cn; hhlaohuili@stu.scau.edu.cn; huangriming@scau.edu.cn; Tel: +86 20 8528 3448

^bGuangdong Polytechnic College, 526100, Zhaoqing, China. E-mail: Yinning.Chen@163.com

^cLonggang No. 2 Vocational School, Shenzhen, 518104, China. E-mail: 345589207@qq.com

^dLaboratory of Pathogenic Biology, Guangdong Medical University, Zhanjiang 524023, China. E-mail: lj2388240@gdmu.edu.cn; Tel: +86 7592388240



Table 1 Monounsaturated fatty acids from marine organisms

Number	Names	Bioactivities	Sources	Reference(s)
1	10-Tricosenoic acid	—	<i>Calyx podatypa</i>	9
2	(6Z)-7-Methyloctadec-6-enoic acid A	—	<i>Holothuria mexicana</i>	10
3	Not given	—	<i>Halichondria panicea</i>	11
4	Not given	—	<i>H. panicea</i>	11
5	Not given	—	<i>Ircinia</i> sp.	12
6	Not given	Antiinflammatory properties	<i>Gracilaria verrucosa</i>	13
7	Not given	—	<i>Ulva fasciata</i>	14
8	Not given	—	<i>U. fasciata</i>	14
9	Not given	—	<i>U. fasciata</i>	14
10	(2E,4S,6S,8S)-2,4,6,8-Tetramethyl-2-undecenoic acid	—	<i>Siphonaria capensis</i>	15
11	Not given	—	<i>S. denticulata</i>	16
12	Not given	—	<i>S. denticulata</i>	16
13	Seco-patulolide	—	unidentified fungal strain	17
14	Not given	—	<i>Sinularia</i> sp.	18

2.2.3 Algae. An extract with antiinflammatory properties from *Gracilaria verrucosa* (Jeju Is., S. Korea) yielded a keto fatty acid **6**.¹³ A bioactivity-directed analysis of *Ulva fasciata* (Aabu-Qir, Mediterranean coast, Egypt) characterized three unsaturated fatty acids **7–9**.¹⁴

2.2.4 Limpets. (2E,4S,6S,8S)-2,4,6,8-Tetramethyl-2-undecenoic acid **10** was obtained from the South African pulmonate mollusc *Siphonaria capensis*.¹⁵ Two fatty acids **11** and **12** were isolated from the siphonariid limpet *Siphonaria denticulata*. The structures were confirmed by synthesis.¹⁶

2.2.5 Microorganisms. An unidentified fungal strain (I96S215), which was obtained from a tissue sample of an

unidentified marine sponge collected in Indonesia, produced seco-patulolide **13**.¹⁷

2.2.6 Corals. The absolute configuration of a unsaturated fatty acid **14**, isolated from *Sinularia* sp. (Ishigaki Is., Okinawa), was determined by the Ohrui–Akasaka method.¹⁸

3 Polyunsaturated fatty acids

3.1 Linear chain polyunsaturated fatty acids

Up to date, there are 24 of total linear chain polyunsaturated fatty acids 15–38 obtained from marine organisms (Table 2 and Fig. 2).

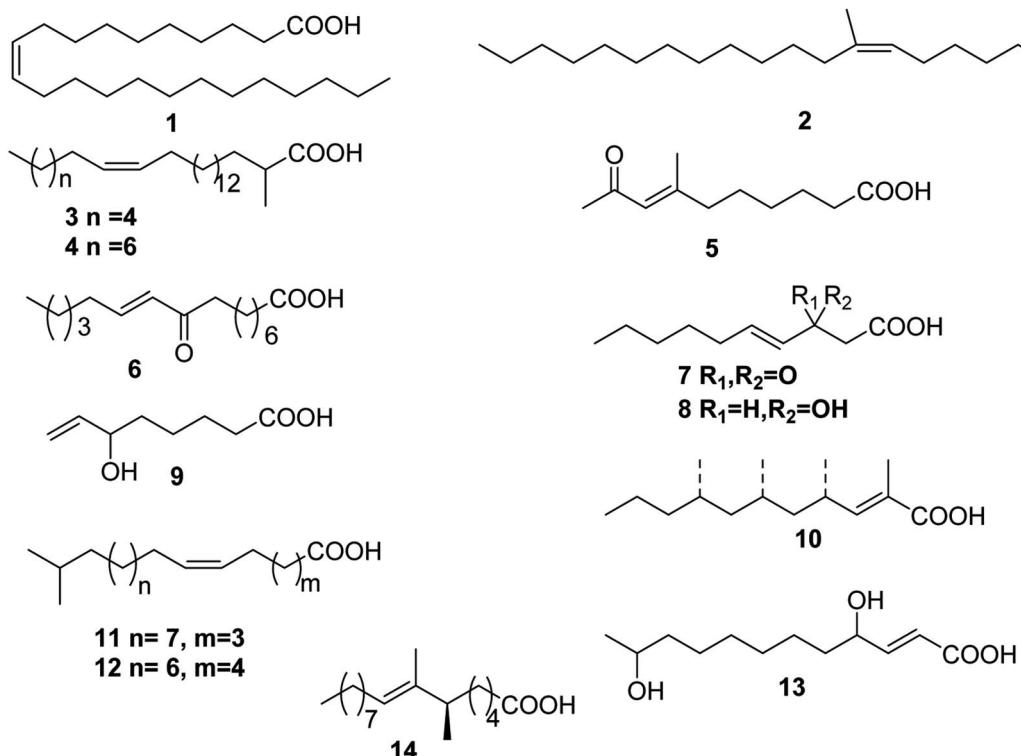


Fig. 1 Structures of monounsaturated fatty acids from marine organisms.



Table 2 Linear polyunsaturated fatty acids from marine organisms

Number	Names	Bioactivities	Sources	Reference(s)
15	Not given	—	<i>Petrosia ficiformis</i>	19
16	Not given	Antimicrobial	<i>Oceanapia</i> sp.	20
17	Carduusyne A	—	<i>Phakellia carduus</i>	21 and 22
18	Petroformynic acid	—	<i>P. ficiformis</i>	23
19	(5Z,7E,9E,14Z,17Z)-Icosa-5,7,9,14,17-pentaenoic acid	—	<i>Ptilota jilicina</i>	24
20	(5E,7E,9E,14Z,17Z)-Icosa-5,7,9,14,17-pentaenoic acid	—	<i>P. jilicina</i>	24
21	5(Z),8(Z),10(E),12(E),14(Z)-Eicosapentaenoic acid	—	<i>Bossiella orbigniana</i>	25
22	(5Z,8Z,11Z,14Z,17Z)-Eicosapentaenoic acid	Inhibiting growth of the green alga <i>Monostroma oxyspermum</i>	<i>Neodilsea yendoana</i>	26
23	(4Z,7Z,9E,11E,13Z,16Z,19Z)-Docosaheptaenoic acid	—	<i>Anadyomene stellata</i>	27
24	10,15-Eicosadienoic acid	—	<i>Haminaea templadoi</i>	28 and 29
25	(5Z,15Z)-5,15-Eicosadienoic acid	—	<i>Calyptogena phaseoliformis</i>	30
26	(5Z,14Z)-5,14-Heneicosadienoic acid	—	<i>C. phaseoliformis</i>	30
27	(5Z,16Z)-5,16-Heneicosadienoic acid	—	<i>C. phaseoliformis</i>	30
28	(5Z,13Z,16Z)-5,13,16-Eicosatrienoic acid	—	<i>C. phaseoliformis</i>	30
29	(5Z,13Z,16Z)-5,13,16,19-Eicosatetraenoic acid	—	<i>C. phaseoliformis</i>	30
30	(5Z,14Z,17Z)-5,14,17-Heneicosatrienoic acid	—	<i>C. phaseoliformis</i>	30
31	7,11,14,17-Eicosatetraenoic acid	Anti-inflammatory	<i>Perna canaliculus</i>	31
32	7,13-Eicosadienoic acid	—	<i>Ophiura sarsi</i>	32
33	7,13,17-Eicosatrienoic acid	—	<i>O. sarsi</i>	32
34	9,15,19-Docosatrienoic acid	—	<i>O. sarsi</i>	32
35	4,9,15,19-Docosatetraenoic acid	—	<i>O. sarsi</i>	32
36	(7Z,9Z,12Z)-Octadeca-7,9,12-trien-5-ynoic acid	—	<i>Liagora farinosa</i>	33
37	4,7,10,13,16,19,22,25-Octacosaoctaenoic acid	—	Marine dinoflagellate species	33
38	7,11-Tetradecadiene-5,9-dynoic acid	—	Marine dinoflagellate species	33

3.1.1 Sponges. One polyacetylene **15** was isolated from *Petrosia ficiformis*, but, as in several earlier examples, the structure was only partially elucidated.¹⁹ The antimicrobial constituent of a Japanese *Oceanapia* sp. was identified as the bis-acetylene **16**.²⁰ One acetylenic acid, carduusyne A **17**, identified as the corresponding ethyl ester, was obtained from a specimen of *Phakellia carduus* obtained from a depth of 350 m by trawling.²¹ The compound **17** has been confirmed by a stereocontrolled synthesis.²² One additional polyacetylene, petroformynic acid **18**, was isolated from both Atlantic and Mediterranean specimens of *Petrosia ficiformis*.²³

3.1.2 Algae. The temperate red alga *Ptilota jilicina* contained (5Z,7E,9E,14Z,17Z)-icosa-5,7,9,14,17-pentaenoic acid **19** and (5E,7E,9E,14Z,17Z)-icosa-5,7,9,14,17-pentaenoic acid **20**, both of which were isolated as the corresponding methyl esters.²⁴ Aqueous extracts of *Bossiella orbigniana* catalyse the enzymatic oxidation of arachidonic acid to bosseopentaenoic acid, 5(Z),8(Z),10(E),12(E),14(Z)-eicosapentaenoic acid **21**, which was isolated from extracts of the alga.²⁵ An allelopathic substance from *Neodilsea yendoana* that inhibited growth of the green alga *Monostroma oxyspermum* was identified as (5Z,8Z,11Z,14Z,17Z)-eicosapentaenoic acid **22**.²⁶ A

polyunsaturated fatty acid, (4Z,7Z,9E,11E,13Z,16Z,19Z)-docosaheptaenoic acid **23**, was encountered in *Anadyomene stellata* from Florida.²⁷

3.1.3 Mollusc. The eicosanoid **24**, which was isolated from *Haminaea templadoi*,²⁸ was synthesized in five steps.²⁹ A series of n-4 polyunsaturated fatty acids including **25–30** were reported from the deep-sea clam *Calyptogena phaseoliformis* (Japan Trench).³⁰ A homologous series of ω-3 polyunsaturated fatty acids, with 7,11,14,17-eicosatetraenoic acid **31** dominating, were isolated as anti-inflammatory components of the green-lipped mussel *Perna canaliculus* (New Zealand).³¹

3.1.4 Echinoderm. Four nonmethylene interrupted polyunsaturated fatty acid derivatives **32–35** were identified in extracts of the brittle star *Ophiura sarsi*.³²

3.1.5 Others. Among the lipids of *Liagora farinosa* were four compounds that can be differentiated by UV absorption and/or the presence of an acetylene functionality. The metabolite, (7Z,9Z,12Z)-octadeca-7,9,12-trien-5-ynoic acid **36**, was ichthyotoxic.³³ Two very long, highly unsaturated fatty acids **37** and **38** were isolated from seven marine dinoflagellate species.³⁴



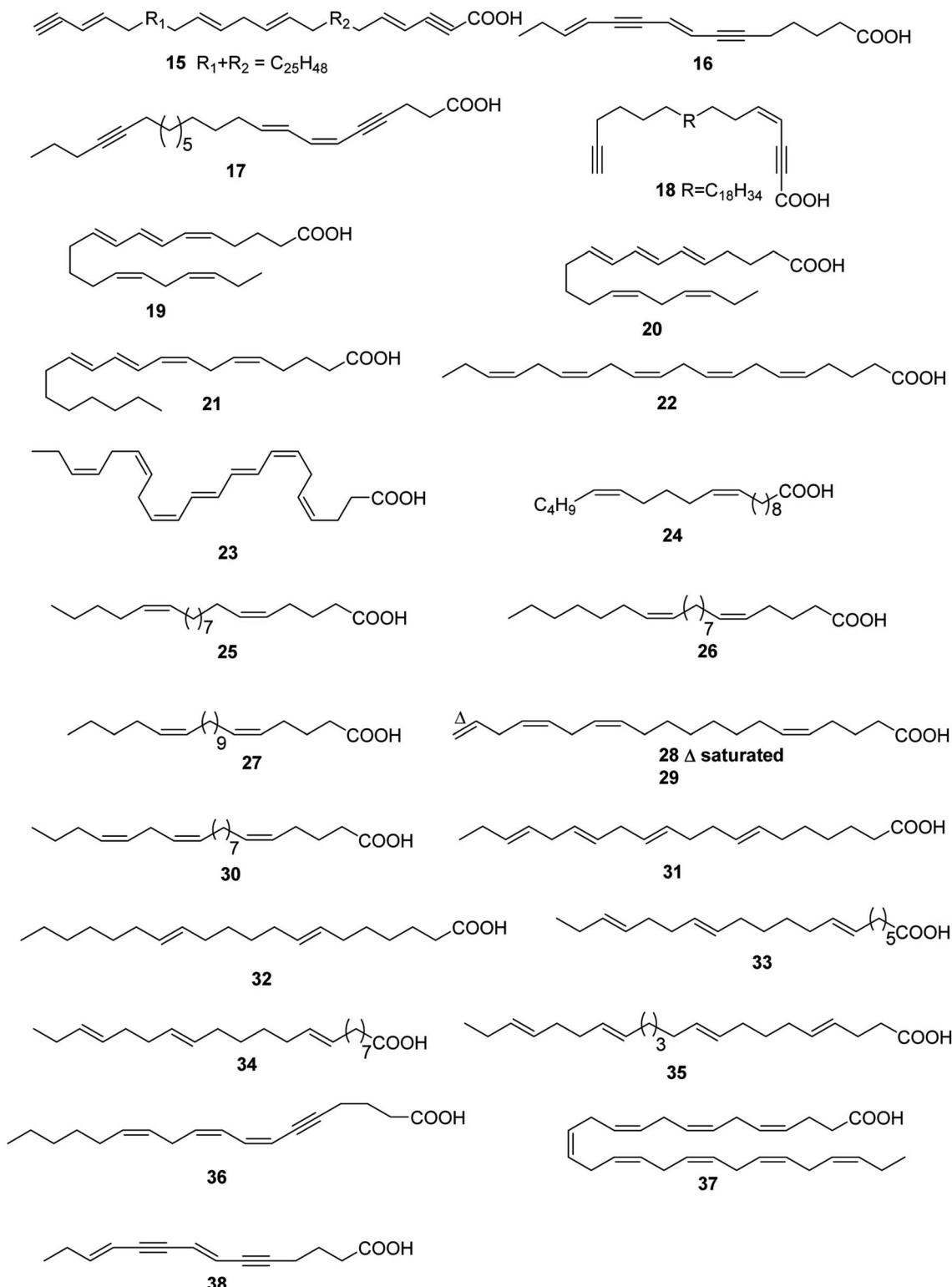


Fig. 2 Structures of linear chain polyunsaturated fatty acids from marine organisms.

3.2 Branched chain polyunsaturated fatty acids

Up to date, there are 109 of total linear chain polyunsaturated fatty acids 39–147 obtained from marine organisms (Tables 3–5 and Fig. 3–5).

3.2.1 Sponges. Acetylenic acids, 39–42, identified as the corresponding ethyl esters, were obtained from a specimen of *Phakellia carduus* obtained from a depth of 350 m by trawling.²¹ Studies on the biosynthesis of the branched fatty acids 43 and

Table 3 Branched chain polyunsaturated fatty acids from sponges

Number	Names	Bioactivities	Sources	Reference(s)
39	Not given	—	<i>P. carduus</i>	21
40	Not given	—	<i>P. carduus</i>	21
41	Not given	—	<i>P. carduus</i>	21
42	Not given	—	<i>P. carduus</i>	21
43	(Z,Z)-25-Methyl-5,9-hexacosadienoic acid	—	<i>Jaspis stellifera</i>	35
44	(Z,Z)-24-Methyl-5,9-hexacosadienoic acid	—	<i>J. stellifera</i>	35
45	(5Z,9Z)-Hexadeca-5,9-dienoic acid	—	<i>Chondrilla nucula</i>	36
46	5,8,10,14,17-Eicosapentaenoic acid	—	<i>Echinochalina mollis</i>	37
47	Not given	—	<i>E. mollis</i>	37
48	4,7,10,12,16,19-Docosahexaenoic acid	—	<i>E. mollis</i>	37
49	Not given	—	<i>E. mollis</i>	37
50	5,9-Eicosadienoic acid	—	<i>Erylus forrnosus</i>	38 and 39
51	5,9-Eicosadienoic acid	—	<i>E. forrnosus</i>	38 and 39
52	Petrosolic acid	Inhibited HIV reverse transcriptase	<i>Petrosia</i> sp.	40
53	Corticatic acid A	Antifungal	<i>Petrosia corticata</i>	41
54	Corticatic acid B	Antifungal	<i>P. corticata</i>	41
55	Corticatic acid C	Antifungal	<i>P. corticata</i>	41
56	Nepheliosyne A	—	<i>Xestospon</i>	42
57	Triangulynic acid	Against leukemia and colon tumour lines	<i>Pellina triangulata</i>	43
58	Pellynic acid	Inhibited inosine monophosphate dehydrogenase <i>in vitro</i>	<i>P. triangulata</i>	44
59	Aztequynol A	—	<i>Petrosia</i> sp.	45
60	Aztequynol B	—	<i>Petrosia</i> sp.	45
61	Osirisyne A	—	<i>Haliclona osiris</i>	46
62	Osirisyne B	—	<i>H. osiris</i>	46
63	Osirisyne C	—	<i>H. osiris</i>	46
64	Osirisyne D	—	<i>H. osiris</i>	46
65	Osirisyne E	—	<i>H. osiris</i>	46
66	Osirisyne F	—	<i>H. osiris</i>	46
67	Aikupikanyne F	—	<i>Callyspongia</i> sp.	20
68	Haliclonyne	—	<i>Haliclona</i> sp.	47
69	Callyspongynic acid	α -glucosidase inhibitor	<i>P. corticata</i>	41, 48 and 49
70	Corticatic acid D	Geranylgeranyltransferase type I inhibitor	<i>P. corticata</i>	41, 48 and 49
71	Corticatic acid E	—	<i>P. corticata</i>	41, 48 and 49
72	(5Z,9Z)-22-Methyl-5,9-tetracosadienoic acid	Cytotoxic activity against mouse Ehrlich carcinoma cells and a hemolytic effect on mouse erythrocytes	<i>Stelletta</i> sp.	50
73	Stellettic acid C	Exhibited marginal to moderate toxicity to five human tumour cell lines	<i>Stelletta</i> sp.	51
74	Not given	Cytotoxic to human leukemia cells	<i>Stelletta</i> sp.	52
75	Petroformynic acid B	Cytotoxic	<i>Petrosia</i>	53
76	Petroformynic acid C	—	<i>Petrosia</i>	53
77	Heterofibrin A ₁	Inhibited lipid droplet formation	<i>Spongia</i> sp.	54
78	Officinoic acid B	—	<i>Spongia officinalis</i>	55
79	Fulvyne A	Against a chloramphenicol-resistant strain of <i>Bacillus subtilis</i>	<i>Haliclona fulva</i>	56
80	Fulvyne B	—	<i>H. fulva</i>	56
81	Fulvyne C	—	<i>H. fulva</i>	56
82	Fulvyne D	—	<i>H. fulva</i>	56



Table 3 (Contd.)

Number	Names	Bioactivities	Sources	Reference(s)
83	Fulvyne E	—	<i>H. fulva</i>	56
84	Fulvyne F	—	<i>H. fulva</i>	56
85	Fulvyne G	—	<i>H. fulva</i>	56
86	Fulvyne H	—	<i>H. fulva</i>	56
87	Fulvyne I	—	<i>H. fulva</i>	56
88	Petrosynic acid A	—	<i>Petrosia</i> sp.	57
89	Petrosynic acid B	—	<i>Petrosia</i> sp.	57
90	Petrosynic acid C	—	<i>Petrosia</i> sp.	57
91	Petrosynic acid D	—	<i>Petrosia</i> sp.	57

44 (from *Jaspis stellifera*) indicated that the unusual long-chain fatty acids were formed by elongation of shorter branched fatty acids, and that methyl branching did not occur after elongation of the chain.³⁵ An unusually short fatty acid, (5Z,9Z)-hexadeca-5,9-dienoic acid **45**, was obtained from *Chondrilla nucula*.³⁶ Relatively large amounts of the eicosanoids **46** and **47** and hydroxy acids **48** and **49** were found in *Echinocalina mollis* from the Coral Sea; they were isolated as the corresponding methyl esters and identified by interpretation of spectral data.³⁷ A stereoselective route to the methyl branched (5Z,9Z)-eicosa-5,9-dienoic acids **50** and **51** found in *Erylus forrnosus*³⁸ has been described.³⁹ Petrosolic acid **52** that inhibited HIV reverse transcriptase was the constituent of a Red Sea *Petrosia* sp.⁴⁰ Corticatic acids A–C **53–55** are antifungal acetylenic acids from *Petrosia corticata* from Japanese waters.⁴¹ Spectroscopic analysis had resulted in a tentative structure for nepheliosyne A **56** from an Okinawan sponge of the genus *Xestospon*.⁴² *Pellina triangulata* from Truk in Micronesia contained triangulynic acid **57**, which is a cytotoxic polyacetylene that was most active against leukemia and colon tumour lines.⁴³ Pellynic acid **58**, which inhibited inosine monophosphate dehydrogenase *in vitro*, was obtained from *Pellina triangulata* from Chuuk (Truk) Atoll.⁴⁴ Aztequynols A **59** and B **60** were C-branched acetylenes from a *Petrosia* sp. from New Caledonia.⁴⁵ A more complex series of highly oxygenated C47 polyacetylenes, osirisynes A–F **61–66**, were isolated as cytotoxins from a Korean specimen of *Haliclona osiris*.⁴⁶ One polyacetylene, aikupikanyne F **67** was obtained from a *Calyspongia* sp. from the Red Sea.²⁰ The polyacetylene carboxylic acid haliclonyne **68** was obtained from a *Haliclona* sp. from the Red Sea.⁴⁷ Japanese specimens of *Calyspongia truncata* yielded the α -glucosidase inhibitor callyspongynic acid **69**⁴⁸ while corticatic acids D **70** and E **71**⁴¹ were isolated from a Japanese *Petrosia corticata* and were found to be geranylgeranyltransferase type I inhibitors.⁴⁹

A cytotoxic fatty acid, (5Z,9Z)-22-methyl-5,9-tetracosadienoic acid **72** was isolated from *Geodinella robusta* collected from the Sea of Okhotsk, Russia.⁵⁰ An undescribed Korean species of *Stelletta* was found to contain a cytotoxic acetylenic acid: stellettic acid C **73** that exhibited marginal to moderate toxicity to five human tumour cell lines.⁵¹ From a seemingly identical *Stelletta* species, collected at a different Korean location, a desmethoxy analogue **74**, was

isolated; it was mildly cytotoxic to human leukemia cells.⁵² The cytotoxic petroformynic acids B **75** and C **76** were obtained from a *Petrosia* species (Katsuo-jim Is., Wakayama Pref., Japan).⁵³ One acetylenic compound heterofibrin A₁ **77** was isolated from a *Spongia* (Heterofibria) sp. collected by dredging in the Great Australian Bight. Heterofibrin A₁ inhibited lipid droplet formation at 10 mM yet was not cytotoxic at similar concentrations.⁵⁴ Officinoic acid B **78** is linear diterpene from *Spongia officinalis* (off Mazara del Vallo, Sicily).⁵⁵ An extract of *Haliclona fulva* (Procida Is., Gulf of Naples, Italy) contained the nine acetylenes fulvyne A–I **79–87**.⁵⁶ Petrosynic acids A–D **88–91** (*Petrosia* sp., Tutuila, American Samoa) all displayed similar activity *versus* various HTCLs and non-proliferative human fibroblasts and hence no therapeutic window is available.⁵⁷

3.2.2 Algae. Malyngic acid **92** is not the acid that is associated with the malyngamides, but it has been shown to be (10E,15Z)-(9S,12R,13S)-9,12,13-trihydroxyoctadeca-10,14-dienoic acid.⁵⁸ Unlike most metabolites from *Lyngbya majuscula*, malyngic acid was found in both shallow- and deep-water varieties. Research on *Laurencia hybrida* indicated that these lipid pools might contain undescribed bioactive metabolites. The antimicrobial constituents (5Z,8E,10E)-11-fomylundeca-5,8,10-trienoic acid **93** and (2Z,5Z,7E,11Z,14Z)-9-hydroxyeicos-2,5,7,11,14-pentaenoic acid **94** might be considered as primary metabolites were it not for their bioactivity.⁵⁹ The additional acyclic diterpene **95** has been reported from *Bifurcaria bifurcate*.⁶⁰ Ptilodene **96** is an eicosanoid from *Ptilota filicina* that inhibited both 5-lipoxygenase and Na⁺/K⁺ ATPase.⁶¹ 12-(S)-Hydroxyeicosapentaenoic acid **97**, which is a potent inhibitor of platelet aggregation, has been isolated in large quantities from *Murrayella periclidios* and has been recognized as the compound previously identified⁶² as 9-hydroxypentaenoic acid **98** from *Laurencia hybrid*.⁶³ The structure of turbinic acid **99**, which is a cytotoxic constituent of *Turbinaria ornata*, was elucidated from spectral data and confirmed by synthesis.⁶⁴ A notable exception was the report of three biologically active eicosanoids, (12R,13R)-dihydroxyeicos-5(Z),8(Z),10(E),14(Z)-tetraenoic acid **100**, (12R,13R)-dihydroxyeicos-5(Z),8(E),10(E),14(Z),17(Z)-pentaenoic acid **101**, and (10R,11R)-dihydroxyoctadeca-6(Z),8(E),12(Z)-trienoic acid **102** that were isolated from the temperate red alga *Farlowia mollis*.⁶⁵ The structure of



Table 4 Branched chain polyunsaturated fatty acids from algae

Number	Names	Bioactivities	Sources	Reference(s)
92	(10E,15Z)-(9S,12R,13S)-9,12,13-Trihydroxyoctadeca-10,14-dienoic acid	—	<i>Lyngbya majuscula</i>	58
93	(5Z,8E,10E)-11-Fomylundeca-5,8,10-trienoic acid	Antimicrobial	<i>Laurencia hybrida</i>	59
94	(2Z,5Z,7E,11Z,14Z)-9-Hydroxyeicosanoic acid	Antimicrobial	<i>L. hybrida</i>	59
95	Acyclizediterpene	—	<i>Bifurcaria bifurcate</i>	60
96	Ptilodene	Inhibited both 5-lipoxygenase and Na ⁺ /K ⁺ TPase	<i>Ptilota filicina</i>	61
97	12-(S)-Hydroxyeicosapentaenoic acid	Inhibitor of platelet aggregation	<i>Murrayella periclados</i>	62
98	9-Hydroxypentaenoic acid	—	<i>Laurencia hybrid</i>	63
99	Turbinic acid	Cytotoxic	<i>Turbinaria ornata</i>	64
100	(12R,13R)-Dihydroxyeicosanoic acid	Modulated fMLP-induced superoxide anion generation in human neutrophils; inhibited the conversion of arachidonic acid to lipoxygenase products by human neutrophils; inhibited the functioning of the dog kidney Na ⁺ /K ⁺ ATPase	<i>Farlowia mollis</i>	65
101	(12R,13R)-Dihydroxyeicosanoic acid	—	<i>F. mollis</i>	65
102	(10R,11R)-Dihydroxyoctadeca-6(Z),8(E),12(Z)-trienoic acid	—	<i>F. mollis</i>	65
103	(5Z,8Z,10E,12R,13R,14Z)-12,13-Dihydroxyeicosanoic acid	—	<i>F. mollis</i>	65
104	(5Z,8Z,10E,12R,13S,14Z)-12,13-dihydroxyeicosanoic acid	—	<i>F. mollis</i>	66
105	(6Z,9E,11E,13E)-9-Formyl-15-hydroxyheptadeca-6,9,11,13-tetraenoic acid	—	<i>Acrosiphonia coalita</i>	67
106	(9E,11E,13E)-9-Formyl-15-hydroxyheptadeca-9,11,13-trienoic acid	—	<i>A. coalita</i>	67
107	(6Z,9E,11E,13E)-9-formyl-15-oxoheptadeca-6,9,11,13-tetraenoic acid	—	<i>A. coalita</i>	67
108	(10E,12Z,14E)-16-Hydroxy-9-oxooctadeca-10,12,14-trienoic acid	—	<i>A. coalita</i>	67
109	(10E,12E,14E)-16-hydroxy-9-oxooctadeca-10,12,14-trienoic acid	—	<i>A. coalita</i>	67
110	(9Z,11R,12S,13S,15Z)-12,13-Epoxy-11-hydroxyoctadeca-9,15-dienoic acid	—	<i>A. coalita</i>	67
111	(9Z,11R,12S,13S)-12,13-Epoxy-11-hydroxyoctadeca-9-enoic acid	—	<i>A. coalita</i>	67
112	(9R,10R,11S,12Z,15Z)-9,10-Epoxy-11-hydroxyoctadeca-12,15-dienoic acid	—	<i>A. coalita</i>	67
113	(9R,10R,11S,12Z)-9,10-Epoxy-11-hydroxyoctadeca-12-enoic acid	—	<i>A. coalita</i>	67
114	Not given	—	<i>Laminaria sinclairii</i>	68
115	Not given	—	<i>L. sinclairii</i>	68
116	9,11-Dodecadienoic acid	—	<i>L. sinclairii</i>	68
117	(13R)-13-hydroxyarachidonic acid	—	<i>Lithothamnion coralloides</i>	69 and 70
118	(12S)-12-Hydroxyeicosatetraenoic acid	—	<i>M. periclados</i>	71
119	(6E)-Leukotriene B ₄	—	<i>M. periclados</i>	71
120	Hepoxilin B ₃	—	<i>M. periclados</i>	71
121	Hepoxilin B ₃	—	<i>M. periclados</i>	71
122	Hepoxilin B ₄	—	<i>M. periclados</i>	71
123	Hepoxilin B ₄	—	<i>M. periclados</i>	71



Table 4 (Contd.)

Number	Names	Bioactivities	Sources	Reference(s)
124	(5R,6S,7E,9E,11Z,14Z)-5,6-Dihydroxyicosa-7,9,11,14-tetraenoic acid	—	<i>Rhodymenia pertusa</i>	72
125	(5R*,6S*,7E,9E,11Z,14Z,17Z)-5,6-Dihydroxyicosa-7,9,11,14,17-pentaenoic acid	—	<i>R. pertusa</i>	72
126	(6E,8Z,11Z,14Z)-5-Hydroxyicosa-6,8,11,14-tetraenoic acid	—	<i>R. pertusa</i>	72
127	(6E,8Z,11Z,14Z,17Z)-5-Hydroxyicosa-6,8,11,14,17-Pentaenoic acid	—	<i>R. pertusa</i>	72
128	8,12-Octadecadienoic acid	—	<i>Corallina officinalis</i>	73
129	(8E,12Z,15Z)-10-Hydroxy-8,12,15-trien-4,6-dienoic acid	—	<i>Caulerpa racemosa</i>	74

a dihydroxy eicosanoid isolated from the red alga *Farlowia mollis* has been revised from (5Z,8Z,10E,12R,13R,14Z)-12,13-dihydroxyeicosa-5,8,10,14-tetraenoic acid **103**⁶⁵ to (5Z,8Z,10E,12R,13S,14Z)-12,13-dihydroxyeicosa-5,8,10,14-tetraenoic acid **104** as a result of the synthesis of the both *threo* and *erythro* isomers.⁶⁶

The green alga *Acrosiphonia coalita* contains the oxylipins coalital, which may be an artefact caused by photoisomerization of the natural product, racemic (6Z,9E,11E,13E)-9-formyl-15-hydroxyheptadeca-6,9,11,13-tetraenoic acid **105**, (9E,11E,13E)-9-formyl-15-hydroxyheptadeca-9,11,13-trienoic acid **106**, (6Z,9E,11E,13E)-9-formyl-15-oxoheptadeca-6,9,11,13-tetraenoic

Table 5 Branched chain polyunsaturated fatty acids from Coelenterate, Marine fungus, Arthropoda, Bacterium

Number	Names	Bioactivities	Sources	Reference(s)
130	Leiopathic acid	—	<i>Leiopathes</i> sp.	75
131	5,9,11,14,17-Eicosapentaenoic acid	—	<i>Leiopathes</i> sp.	75
132	5,9,11,14,17-Eicosapentaenoic acid (11R)	—	<i>Leiopathes</i> sp.	75
133	Hydroxyeicosatetraenoic acid	—	<i>Plexaurella dichotoma</i>	76
134	(5Z,9Z)-14-methylpentadeca-5,9-dienoic acid	Inhibited the growth of Gram positive bacteria	<i>Eunicea succinea</i>	77
135	6,9,12,16,18-Tetracosapentaenoic acid	Inhibited tube-formation in a human endothelial cell line model of angiogenesis	<i>Sinularia numerosa</i>	78
136	Dendryphiellie acid A	—	<i>Dendryphiella salina</i>	79 and 80
137	Dendryphiellie acid B	—	<i>D. salina</i>	79 and 80
138	Curvularic acid	—	<i>Curvularia</i> sp.	81
139	2,4-Decadienoic acid	—	<i>Xylaria</i> sp.	82
140	(5Z,8R,9E,11Z,14Z,17Z)-8-hydroxyeicosa-5,9,11,14,17-pentaenoic acid	—	<i>Balanus balanoides, Eliminus modestus</i>	83
141	8,13-Dihydroxyicosapentaenoic acid	A muscle stimulatory factor in the barnacle <i>Balanus balanus</i>	<i>Balanus balanus</i>	84
142	(9Z,12Z)-7-hydroxyoctadeca-9,12-dien-5-ynoic acid	Ichthyotoxic	<i>L. farinosa</i>	33
143	Macrolactic acid	—	Unidentified Gram-positive bacterium	85
144	Isomacrolactic acid	—	Unidentified Gram-positive bacterium	85
145	Ieodomycin C	Antimicrobial	<i>Bacillus</i> sp.	86
146	Ieodomycin D	—	<i>Bacillus</i> sp.	86
147	Linieolide B	Antibacterial; antifungal	<i>Bacillus</i> sp.	87 and 88



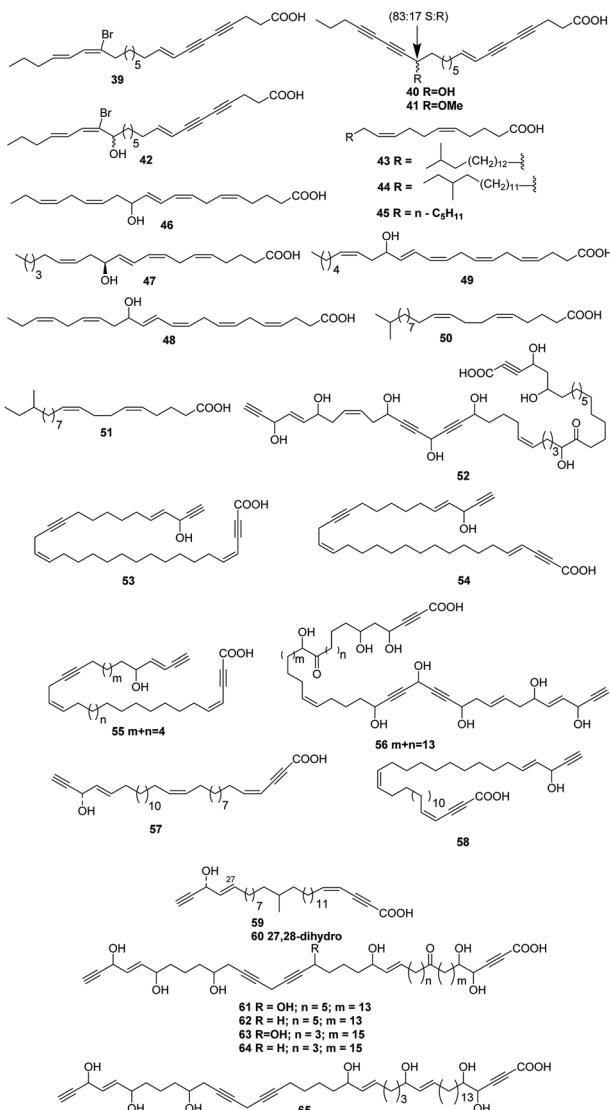
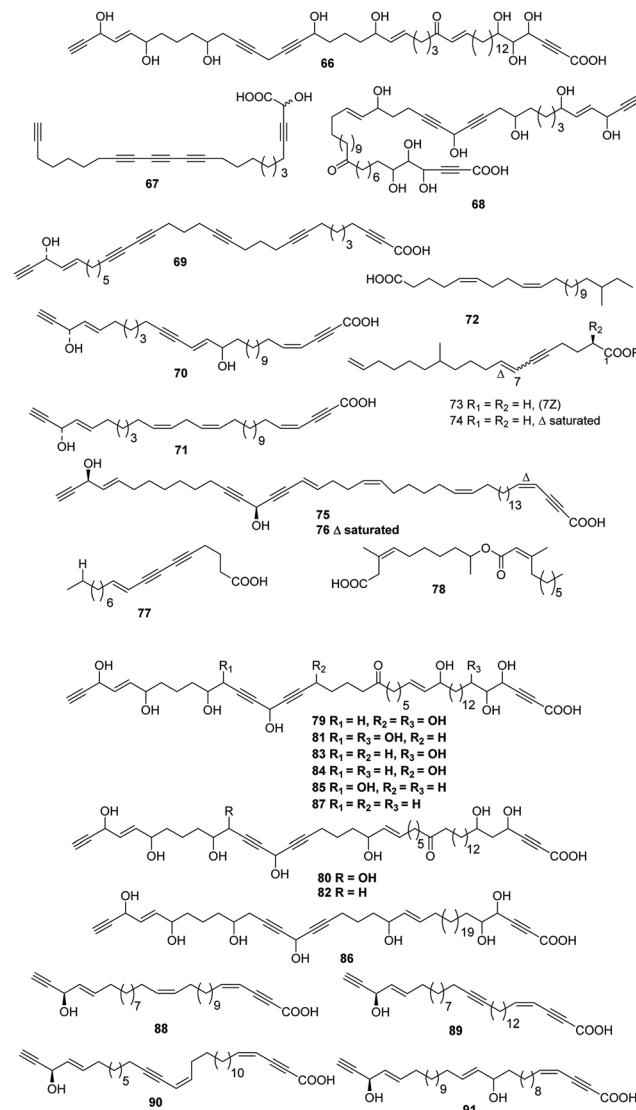


Fig. 3 Structures of branched chain polyunsaturated fatty acids from sponges.

acid **107**, $(10E,12Z,14E)$ -16-hydroxy-9-oxooctadeca-10,12,14-trienoic acid **108**, $(10E,12E,14E)$ -16-hydroxy-9-oxooctadeca-10,12,14-trienoic acid **109**, $(9Z,11R,12S,13S,15Z)$ -12,13-epoxy-11-hydroxyoctadeca-9,15-dienoic acid **110**, $(9Z,11R,12S,13S)$ -12,13-epoxy-11-hydroxyoctadeca-9-enoic acid **111**, $(9R,10R,11S,12Z,15Z)$ -9,10-epoxy-11-hydroxyoctadeca-12,15-dienoic acid **112**, and $(9R,10R,11S,12Z)$ -9,10-epoxy-11-hydroxyoctadeca-12-enoic acid **113**, the acids all being isolated as the corresponding methyl esters.⁶⁷ Three divinyl ethers, **114**–**116**, were isolated along with a number of hydroxylated fatty acids from the Oregon brown alga *Laminaria sinclairii* and were identified by interpretation of spectral evidence.⁶⁸ The absolute stereochemistry of $(13R)$ -13-hydroxyarachidonic acid **117**, which is a known eicosanoid from *Lithothamnion coralloides*,⁶⁹ was determined by degradation and its biosynthesis from arachidonic acid was studied.⁷⁰

The Caribbean alga *Murrayella periclados* contains a number of eicosanoids that include $(12S)$ -12-hydroxyeicosatetraenoic



acid **118**, $(6E)$ -leukotriene B₄, **119** and *erythro* and *threo* isomers of hepxolins B₃, **120**/**121** and B₄, **122**/**123**.⁷¹ Four oxylipins $(5R,6S,7E,9E,11Z,14Z)$ -5,6-dihydroxyicos-7,9,11,14-tetraenoic acid **124**, $(5R^*,6S^*,7E,9E,11Z,14Z,17Z)$ -5,6-dihydroxyicos-7,9,11,14,17-pentaenoic acid **125**, $(6E,8Z,11Z,14Z)$ -5-hydroxyicos-6,8,11,14-tetraenoic acid **126**, and $(6E,8Z,11Z,14Z,17Z)$ -5-hydroxyicos-6,8,11,14,17-pentaenoic acid **127** were isolated from *Rhodymenia pertusa*.⁷² An oxylipin **128** was obtained from *Aspergillus flavus*, (red alga *Corallina officinalis*, Yantai, China).⁷³ Studies on a *Caulerpa racemosa* (Zhanjiang coastline, China) led to the isolation of the acetylenic fatty acid $(8E,12Z,15Z)$ -10-hydroxy-8,12,15-trien-4,6-dienoic acid **129**.⁷⁴

3.2.3 Coelenterate. Leiopathic acid **130** and two known eicosanoids, **131** and **132**, were isolated from a black coral, *Leiopathes* sp., collected at St Paul Island in the South India Ocean.⁷⁵ $(11R)$ -Hydroxyeicosatetraenoic acid **133**, a proposed intermediate on the pathway to prostanoids in coelenterates, has



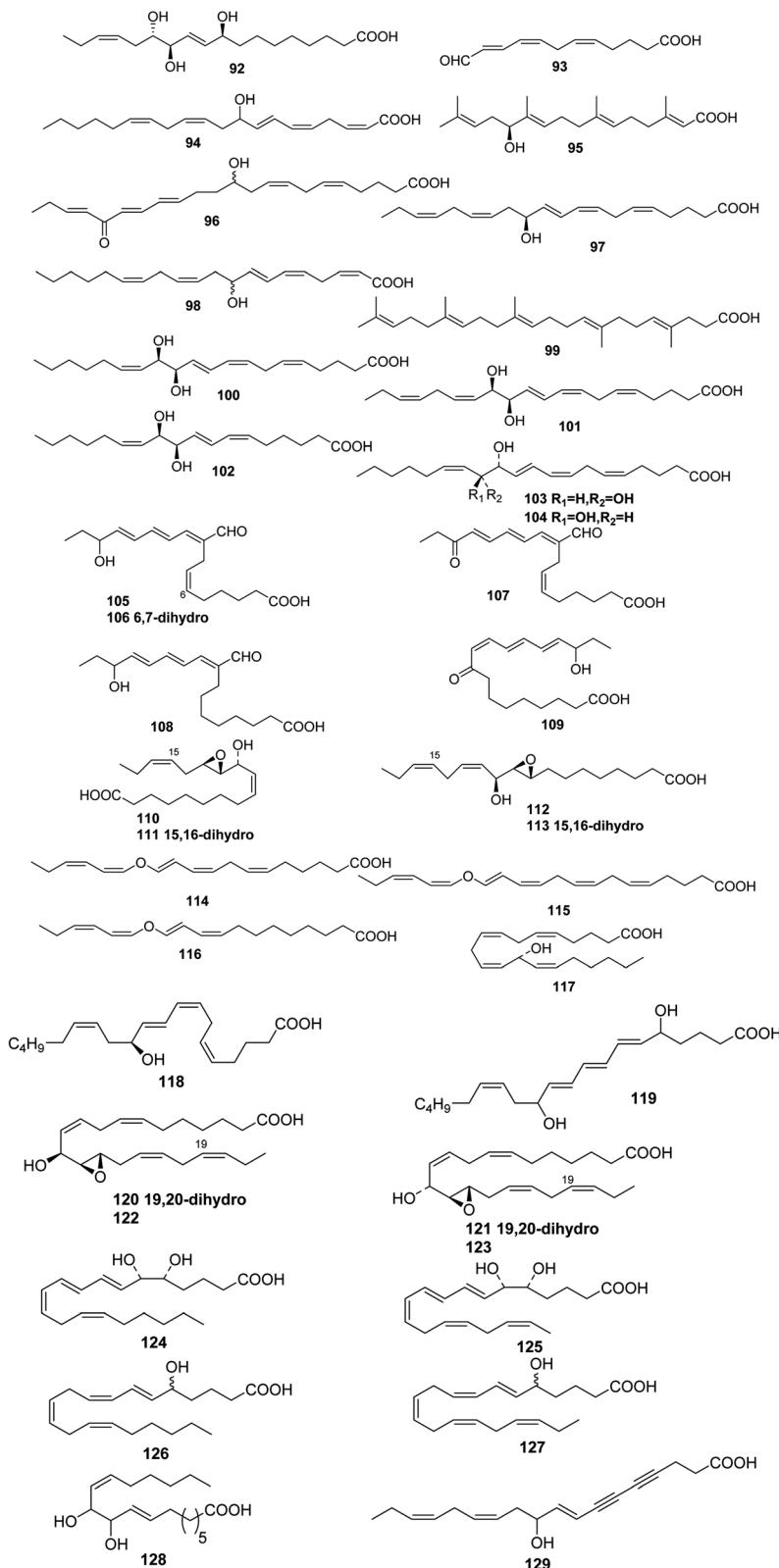


Fig. 4 Structures of branched chain polyunsaturated fatty acids from marine algae.

been found in the gorgonian *Plexaurella dichotoma*.⁷⁶ The gorgonian *Eunicea succinea* contained (5Z,9Z)-14-methylpentadeca-5,9-dienoic acid **134**, which inhibited the growth of Gram positive bacteria.⁷⁷

Oxylipin **135**, isolated by bioassay-directed fractionation (*Sinularia numerosa*, Kagoshima Prefecture, Japan), inhibited tube-formation in a human endothelial cell line model of angiogenesis.⁷⁸

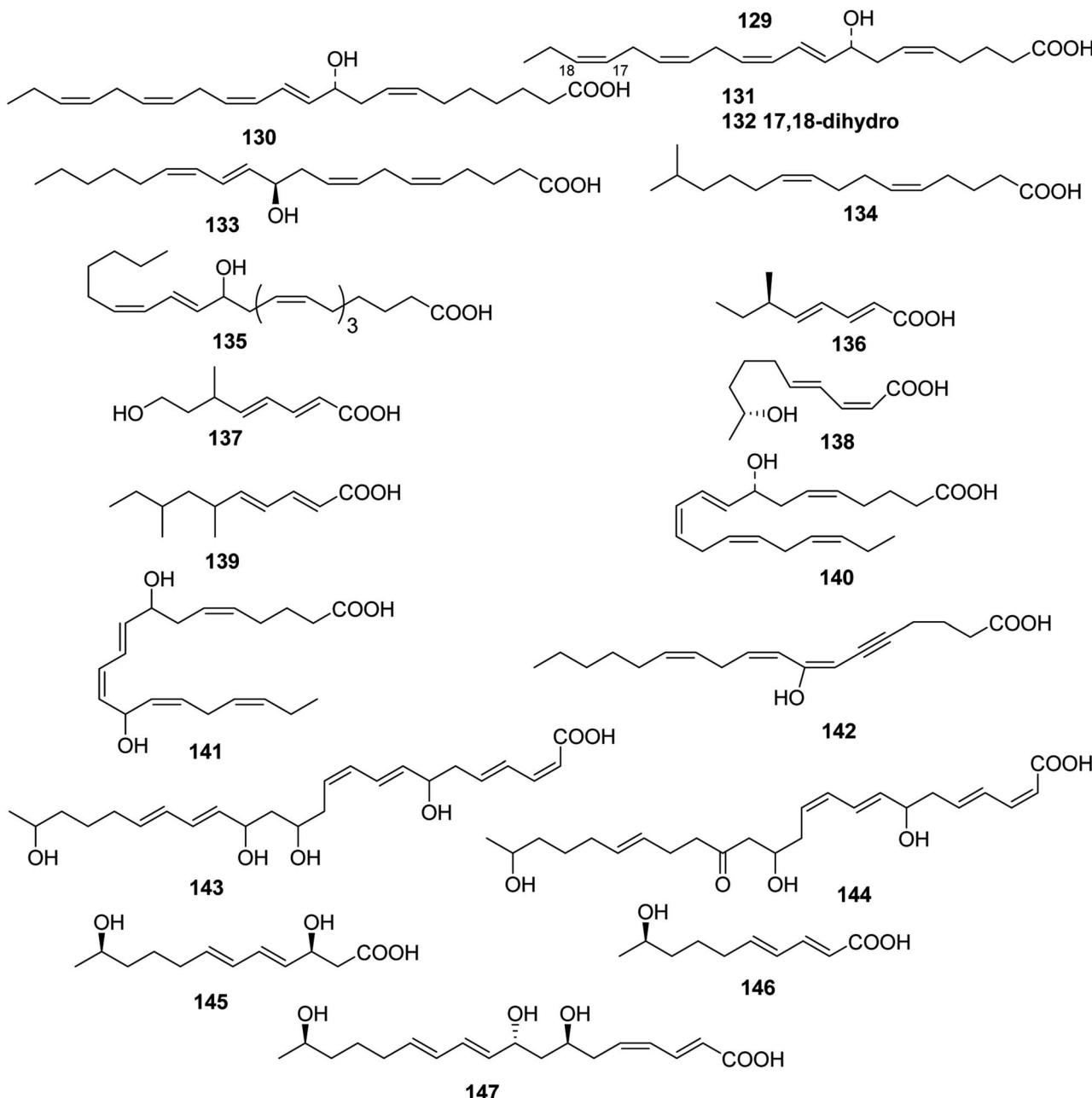


Fig. 5 Structures of branched chain polyunsaturated fatty acids from Coelenterate, Marine fungus, Arthropoda, Bacterium.

3.2.4 Marine fungus. The marine deuteromycete *Dendryphiella salina* produced an unusual group of trinor-eremophilane and eremophilane derivatives.⁷⁹ The structures of dendryphiellic acids A 136 and B 137 were proposed on the basis of spectral and chemical studies as well as comparison of their spectral data with those of dendryphiellin A.⁸⁰ A *Curvularia* sp. (sea fan *Annella* species, Similan Islands, Phangnga, Thailand) yielded the metabolites curvularic acid 138.⁸¹ The lipid 139 was obtained from *Xylaria* sp.⁸²

3.2.5 Arthropoda. The structure of the hatching factor of the barnacles *Balanus balanoides* and *Eliminus modestus* has been confirmed by synthesis to be (5Z,8R,9E,11Z,14Z,17Z)-8-

hydroxyeicosa-5,9,11,14,17-pentaenoic acid 140.⁸³ 8,13-Dihydroxyeicosapentaenoic acid 141 was identified as a muscle stimulatory factor in the barnacle *Balanus balanus*.⁸⁴

3.2.6 Bacterium. The metabolite, (9Z,12Z)-7-hydroxyoctadeca-9,12-dien-5-ynoic acid 142, was ichthyotoxic.⁸³ An unidentified Gram-positive bacterium from a deep-sea sediment core produced macrolactic acid 143 and iso-macrolactic acid 144.⁸⁵ The fatty acids, ieodomycins C 145 and D 146 from *Bacillus* sp. (sediment, Ieodo, South Korea) had broad spectrum antimicrobial activity.⁸⁶ *Bacillus* sp. (sediment, Ieodo Reef, S. Korea)⁸⁷ produced the unsaturated fatty acid linieadolide B 147, with modest antibacterial and antifungal activity.⁸⁸



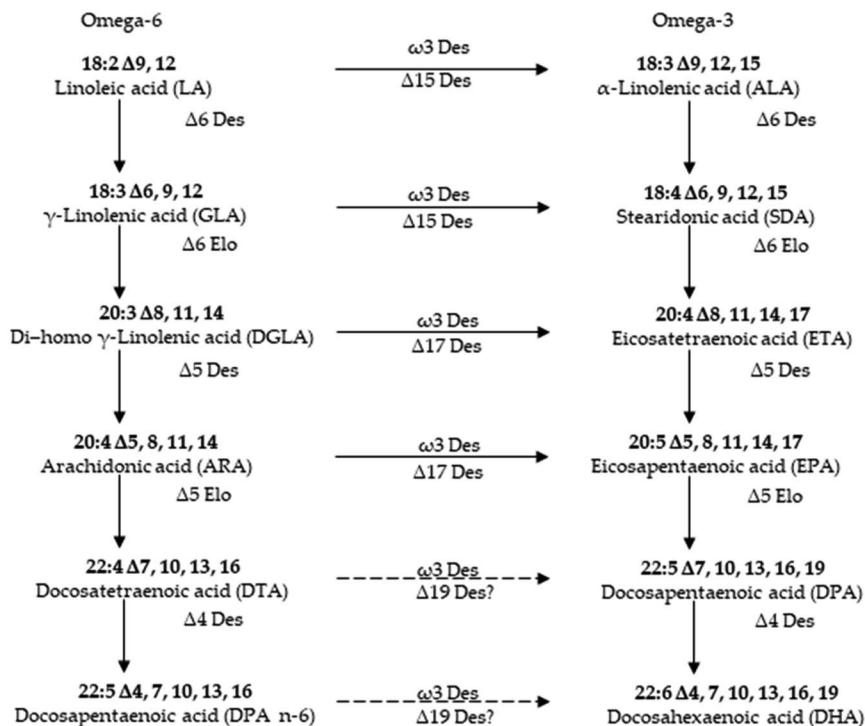


Fig. 6 Pathway for the biosynthesis of long chain polyunsaturated fatty acids in microalgae.

4 Biosynthetic pathways

PUFAs are gaining importance due to their innumerable health benefits. The most common source of PUFAs is of marine origin. Hence, understanding their biosynthesis in marine origin has attained prominence in recent years.^{89,90} Rabbitfish *Siganus canaliculatus* was the first marine teleost demonstrated to have the ability to biosynthesize C20–22 long-chain polyunsaturated fatty acid (LC-PUFA) from C18 PUFA precursors, which is generally absent or low in marine teleosts.⁹¹ The marine diatom *Phaeodactylum tricornutum* accumulates eicosapentaenoic acid (EPA, 20:5n-3) as its major component of fatty

acids. To improve the EPA production, delta 5 desaturase, which plays a role in EPA biosynthetic pathway, was characterized in marine diatom *Phaeodactylum tricornutum*.⁹⁰ There is currently considerable interest in understanding how the biosynthetic pathways of highly unsaturated fatty acids (HUFA) are regulated in fish. The aim is to know if it is possible to replace fish oils (FO), rich in HUFA, by vegetable oils (VO), poor in HUFA and rich in their 18 carbon fatty acid precursors, in the feed of cultured fish species of commercial importance.⁹² Although many better insights into the synthesis of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in marine microalgae,⁹³ there are still a little known about

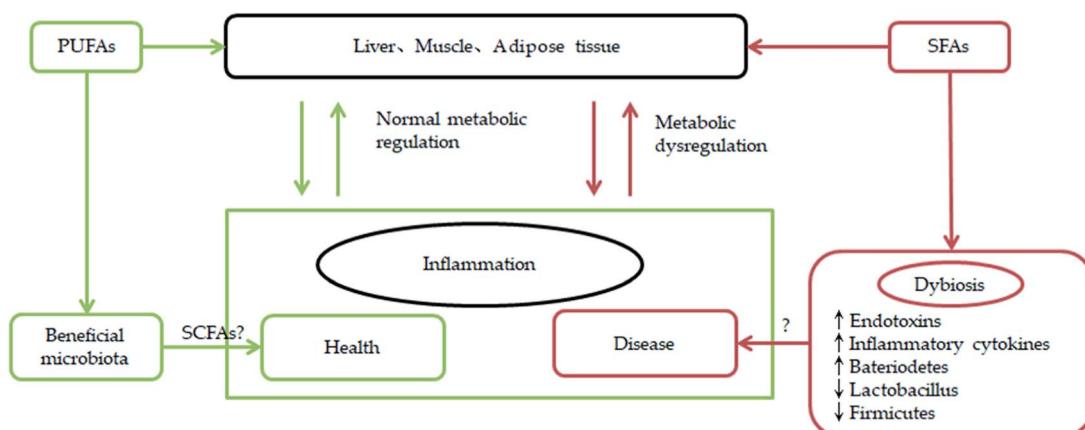


Fig. 7 Impact of SFA and PUFA on gut microbiota and metabolic regulation.

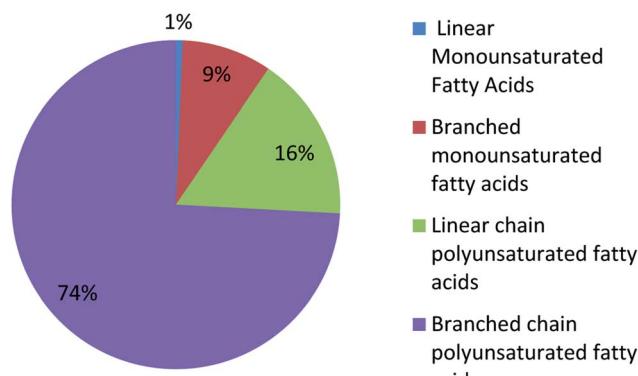


Fig. 8 The distribution of UFAs reported from marine organisms.

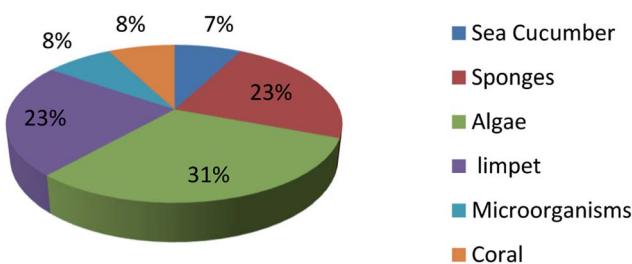


Fig. 9 Origin of branched monounsaturated fatty acids.

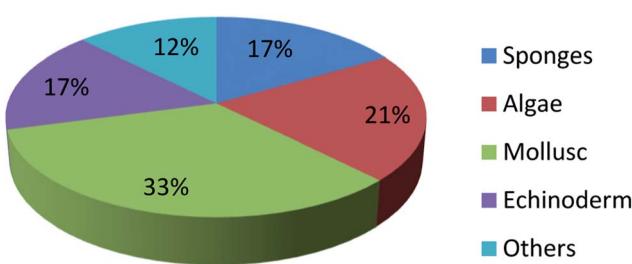


Fig. 10 Origin of linear chain polyunsaturated fatty acids.

biosynthetic processes of most isolated UFAs of marine resources.^{70,94} Thus, more investigation should be carried out for these marine derived UFAs in the coming researches (Fig. 6).

5 Beneficial application

It is well-known that polyunsaturated fatty acids n-3 (PUFAn-3) are very important for human health and nutrition.¹ As an example, highly unsaturated long-chain omega-3 fatty acids, derived from the liver of white lean fish, flesh of fatty fish, and blubber of marine mammals, exhibit important biological activities.⁹⁵ They also serve as the building block fatty acids in the brain, retina, and other organs with electrical activity. Hence, inclusion of oils containing docosahexaenoic acid (DHA) in the diet of pregnant and lactating women as well as infants is encouraged.⁹⁵

In addition, some polyunsaturated fatty acids from marine microalgae are found to modulate lipid metabolism disorders and gut microbiota.⁹⁶ According to the survey results, high saturated fatty acid and high monounsaturated fatty acid diets have an adverse effect on the gut microbiota and high saturated fatty acids are associated with unhealthy metabolic status, while polyunsaturated fatty acid does not have a negative impact on gut microbiota.⁹⁷ Through previous studies we find that connecting with gut microbiota, PUFAs can be more beneficial for human health. For example, increasing anti-obesogenic microbial species in the gut microbiota population by appropriate n-3 PUFAs can be an effective way to control or prevent metabolic diseases.⁹⁸ Furthermore, a link has been established between n-3 PUFAs and gut microbiota especially with respect to inflammation (Fig. 7). A few related researchs show that after omega-3 PUFA supplementation, *Faecalibacterium*, often associated with an increase in the Bacteroidetes and butyrate-producing bacteria belonging to the Lachnospiraceae family, has decreased. Omega-3 PUFAs perform a positive action on diseases by reverting the microbiota composition and increasing the production of anti-inflammatory compounds like short-chain fatty acids.⁹⁹ According to the link between n-3 PUFAs and gut microbiota, which is associated with inflammation, some scholars proposing that an optimal level of LC-PUFAs nurtures the suitable gut microbiota that will prevent dysbiosis. The synergy between optimal LC-PUFAs and gut microbiota helps the immune system overcome the immunosuppressive tumour microenvironment.¹⁰⁰



Fig. 11 Origin of branched chain polyunsaturated fatty acids.



Although many scholars have devoted themselves to the study of polyunsaturated fatty acids, they are limited to the more famous unsaturated fatty acids. There is still lack of investigation of the beneficial application of these polyunsaturated fatty acid derivatives with similar structural characteristics. Thus, more investigation should focus on fatty acid physiological roles and applications in human health and disease and the interaction with gut microbiota.¹⁰¹

6 Conclusions

UFAs are ubiquitous in many marine organisms.^{3,102,103} Although these UFA secondary metabolites have been obtained since the early 20th century, they only recently draw significant interests because of the diverse range of their biological and nutritional properties.¹⁰⁴ However, there is still lack of a comprehensive review about the structural characterizations, biological and nutritional properties, proposed biosynthetic processes, and beneficial application of marine derived UFAs. 1978 to 2018, the main structural types of UFAs obtained from marine organisms is branched chain PUFAs, accounting for 74% of the total (Fig. 8), the main natural source of branched monounsaturated fatty acids isolated from marine organisms is coral, accounting for 31% (Fig. 9), while linear chain polyunsaturated fatty acids obtained from marine organisms is mollusc, accounting for 33% (Fig. 10), the preponderant natural marine source of PUFAs is arthropoda, accounting for 49% (Fig. 11). Although omega-3 fatty acid,⁶ eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from marine organisms, have dramatically increased as excellent sources of nutrients, it is indicated that the biological activities of most of the UPAs are not investigated (Tables 1–3), and the little known about the biosynthetic pathways of these isolated UPAs. In addition, there is no report about new UFAs isolated from marine resources during 2016 to 2018. Thus, the further investigation of marine derived PUFAs should focus on their and beneficial application mediated by gut microbiota.

Conflicts of interest

The authors declare no conflict of interest.

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Notes and references

- E. B. Rimm, L. J. Appel, S. E. Chiuve, L. Djousse, M. B. Engler, P. M. Kris-Etherton, D. Mozaffarian, D. S. Siscovick, A. H. Lichtenstein, C. L. C. Hilt, C. E. Prevention, C. C. D. Young, C. C. S. Nursing and C. C. Cardiology, *Circulation*, 2018, **138**, E35–E47.
- M. E. Riveros and M. A. Retamal, *Front. Physiol.*, 2018, **9**, 693.
- A. Tsoupras, R. Lordan, K. Shiels, S. K. Saha, C. Nasopoulou and I. Zabetakis, *Mar. Drugs*, 2019, **17**.
- E. Alexandri, A. Raheel, H. Siddiqui, M. I. Choudhary, C. G. Tsiafoulis and I. P. Gerolanthassis, *Molecules*, 2017, **22**, 1633–1671.
- T. Gluck and P. Alter, *Vasc. Pharmacol.*, 2016, **82**, 11–19.
- D. S. Im, *Eur. J. Pharmacol.*, 2016, **785**, 36–43.
- P. Kuppusamy, I. Soundharajan, S. Srivopalram, M. M. Yusoff, G. P. Maniam, N. Govindan and K. C. Cho, *Indian J. Geo-Mar. Sci.*, 2017, **46**, 663–667.
- M. Masson, T. Loftsson and G. G. Haraldsson, *Pharmazie*, 2000, **55**, 172–177.
- N. M. Carballeira, M. Pagan and A. D. Rodriguez, *J. Nat. Prod.*, 1998, **61**, 1049–1052.
- N. M. C. Carballeira, C. Clarisa and A. Sostre, *J. Nat. Prod.*, 1996, **59**, 1076–1078.
- M. Perpelescu, M. Tsuda, M. Suzuki, S. Yoshida and J. Kobayashi, *Nat. Med.*, 2004, **58**, 86.
- I. I. Tatli, F. Kong, X. Feng, G. Carter, K. V. Rao and M. T. Hamann, *J. Chem. Res.*, 2008, 50–51, DOI: 10.3184/030823408x287131.
- H. T. Dang, H. J. Lee, E. S. Yoo, P. B. Shinde, Y. M. Lee, J. Hong, D. K. Kim and J. H. Jung, *J. Nat. Prod.*, 2008, **71**, 232–240.
- G. S. E. Abou-ElWafa, M. Shaaban, K. A. Shaaban, M. E. E. El-Naggar and H. Laatsch, *Z. Naturforsch., B: J. Chem. Sci.*, 2009, **64**, 1199–1207.
- D. R. D.-C. Beukes and T. Michael, *Tetrahedron*, 1999, **55**, 4051–4056.
- N. M. Carballeira, H. Cruz, C. A. Hill, J. J. De Voss and M. Garson, *J. Nat. Prod.*, 2001, **64**, 1426–1429.
- C. J. Smith, D. Abbanat, V. S. Bernan, W. M. Maiese, M. Greenstein, J. Jompa, A. Tahir and C. M. Ireland, *J. Nat. Prod.*, 2000, **63**, 142–145.
- K. Watanabe, R. Makino, H. Takahashi, K. Iguchi, H. Ohnri and K. Akasaka, *Chem. Pharm. Bull.*, 2008, **56**, 861–863.
- G. Cimino, A. De Giulio, S. De Rosa, S. De Stefano and G. Sodano, *J. Nat. Prod.*, 1985, **48**, 22–27.
- S. Matsunaga, Y. Okada, N. Fusetani and R. W. M. Van Soest, *J. Nat. Prod.*, 2000, **63**, 690–691.
- R. A. C. Barrow and J. Robert, *Aust. J. Chem.*, 1994, **47**, 1901–1918.
- P. D. Charoenying, D. Huw, D. McKerrecher and R. J. K. Taylor, *Tetrahedron Lett.*, 1996, **37**, 1913–1916.
- Y. G. Guo, M. Gavagnin, C. Salierno and G. Cimino, *J. Nat. Prod.*, 1998, **61**, 333–337.
- A. G. Lopez and H. William, *Lipids*, 1987, **22**, 190–194.



25 J. R. D. I. R. Burgess, I. Roger, R. S. Jacobs and A. Butler, *Lipids*, 1991, **26**(2), 162–165.

26 M. Suzuki, I. Wakana, T. Denboh and M. Tatewaki, *Phytochemistry*, 1996, **43**, 63–65.

27 M. V. B. Mikhailova, L. Debra, M. L. Wise, W. H. Gerwick, J. N. Norris and R. S. Jacobs, *Lipids*, 1995, **30**, 583–589.

28 N. M. Carballeira, E. Anastacio, J. Salva and M. J. Ortega, *J. Nat. Prod.*, 1992, **55**, 1783–1786.

29 B. A. Kulkarni, A. Chattopadhyay and V. R. Mamdapur, *J. Nat. Prod.*, 1994, **57**, 537–538.

30 H. Saito, *J. Chromatogr. A*, 2007, **1163**, 247–259.

31 A. P. Treschow, L. D. Hodges, P. F. A. Wright, P. M. Wynne, N. Kalafatis and T. A. Macrides, *Comp. Biochem. Physiol., Part B: Biochem. Mol. Biol.*, 2007, **147**, 645–656.

32 D. Sato, Y. Ando, R. Tsujimoto and K. Kawasaki, *Lipids*, 2001, **36**, 1372–1375.

33 V. J. Paul and W. Fenical, *Tetrahedron Lett.*, 1980, **21**, 3327–3330.

34 M. P. V. Mansour, K. John, D. G. Holdsworth, A. E. Jackson and S. I. Blackburn, *Phytochemistry*, 1999, **50**, 541–548.

35 N. T. Carballeira, E. Janice, E. Ayanoglu and C. Djerassi, *J. Org. Chem.*, 1986, **52**, 2751–2756.

36 N. M. Carballeira and L. Maldonado, *Lipids*, 1986, **21**, 470–471.

37 A. Guerriero, M. D'Ambrosio, F. Pietra, O. Ribes and D. Duhet, *J. Nat. Prod.*, 1990, **53**, 57–61.

38 N. M. Carballeira and V. Negron, *J. Nat. Prod.*, 1991, **54**, 305–309.

39 B. A. Kulkarni, A. Chattopadhyay and V. R. Mamdapur, *Nat. Prod. Lett.*, 1993, **3**, 251–255.

40 S. Isaacs, Y. Kshman, S. Loya, A. Hizi and Y. Loya, *Tetrahedron*, 1993, **49**, 10435–10438.

41 H.-Y. Li, S. Matsunaga and N. Fusteanu, *J. Nat. Prod.*, 1994, **57**, 1464–1467.

42 J. Kobayashi, K. Naitoh, K. Ishida, H. Shigemori and M. Ishibashi, *J. Nat. Prod.*, 1994, **57**, 1300–1303.

43 J.-R. H. Dai, F. Yali, J. H. Cardellina II, G. N. Gray and M. R. Boyd, *J. Nat. Prod.*, 1996, **59**, 860–865.

44 X. Fu, S. A. Abbas, F. J. Schmitz, I. Vidavsky, M. L. Gross, M. Laney, R. C. Schatzman and R. D. Cabuslay, *Tetrahedron*, 1997, **53**, 799–814.

45 A. Guerriero, C. Debitus, D. Laurent, M. D'Ambrosio and F. Pietra, *Tetrahedron Lett.*, 1998, **39**, 6395–6398.

46 J. Shin, Y. Seo, K. W. Cho, J. R. Rho and V. J. Paul, *Tetrahedron*, 1998, **54**, 8711–8720.

47 L. Chill, A. Miroz and Y. Kashman, *J. Nat. Prod.*, 2000, **63**, 523–526.

48 Y. Nakao, T. Uehara, S. Matunaga, N. Fusetani and R. W. M. van Soest, *J. Nat. Prod.*, 2002, **65**, 922–924.

49 S. Nishimura, S. Matsunaga, M. Shibasaki, K. Suzuki, N. Harada, H. Naoki and N. Fusetani, *J. Nat. Prod.*, 2002, **65**, 1353–1356.

50 T. N. Makarieva, E. A. Santalova, I. A. Gorshkova, A. S. Dmitrenok, A. G. Guzii, V. I. Gorbach, V. I. Svetashev and V. A. Stonik, *Lipids*, 2002, **37**, 75–80.

51 Q. C. Zhao, T. A. Mansoor, J. K. Hong, C. O. Lee, K. S. Im, D. S. Lee and J. H. Jung, *J. Nat. Prod.*, 2003, **66**, 725–728.

52 H. S. Lee, J. R. Rho, C. J. Sim and J. Shin, *J. Nat. Prod.*, 2003, **66**, 566–568.

53 C. Okamoto, Y. Nakao, T. Fujita, T. Iwashita, W. M. van Soest, N. Fusetani and S. Matsunaga, *J. Nat. Prod.*, 2007, **70**, 1816–1819.

54 A. A. Salim, J. Rae, F. Fontaine, M. M. Conte, Z. Khalil, S. Martin, R. G. Parton and R. J. Capon, *Org. Biomol. Chem.*, 2010, **8**, 3188–3194.

55 E. Manzo, M. L. Ciavatta, G. Villani, M. Varcamonti, S. M. Abu Sayem, R. van Soest and M. Gavagnin, *J. Nat. Prod.*, 2011, **74**, 1241–1247.

56 G. Nuzzo, M. L. Ciavatta, G. Villani, E. Manzo, A. Zanfardino, M. Varcamonti and M. Gavagnin, *Tetrahedron*, 2012, **68**, 754–760.

57 E. J. Mejia, L. B. Magranet, N. J. De Voogd, K. TenDyke, D. Y. Qiu, Y. Y. Shen, Z. R. Zhou and P. Crews, *J. Nat. Prod.*, 2013, **76**, 425–432.

58 J. H. Cardellina II and R. E. Moore, *Tetrahedron*, 1980, **36**, 993–996.

59 M. D. Higgs and L. J. Mulheirn, *Tetrahedron*, 1981, **37**, 4259–4262.

60 L. Z. Semmak, Abdelfetta, R. Valls, B. Banaigs, G. Jeanty and C. Francisco, *Phytochemistry*, 1988, **27**, 2347–2349.

61 A. G. Lopez and H. William, *Tetrahedron Lett.*, 1988, **29**, 1505–1506.

62 M. D. Higgs, *Tetrahedron*, 1981, **37**, 4255–4258.

63 M. G. Bernart and H. William, *Tetrahedron Lett.*, 1988, **29**, 2015–2018.

64 F. Asari, T. Kusumi and H. Kakisawa, *J. Nat. Prod.*, 1989, **52**, 1167–1169.

65 M. L. J. Solem, D. Zhi and W. H. Gerwick, *Lipids*, 1989, **24**, 256–260.

66 S. Lumin and J. R. Falck, *Tetrahedron Lett.*, 1990, **31**, 2971–2974.

67 M. W. Bernart, G. G. Whatley and W. H. Gerwick, *Nat. Prod.*, 1993, **56**(2), 245–259.

68 P. J. G. Proteau and H. William, *Lipids*, 1993, **28**, 783–787.

69 A. Guerriero, M. D'Ambrosio and F. Pietra, *Helv. Chim. Acta*, 1990, **73**, 2183–2189.

70 W. H. Gerwick, P. Aasen and M. Hamberg, *Phytochemistry*, 1993, **34**, 1029–1033.

71 M. W. G. Bernari and H. William, *Phytochemistry*, 1994, **36**, 1233–1240.

72 Z. D. K. Jiang, O. Sharon and W. H. Gerwick, *Phytochemistry*, 2000, **53**, 129–133.

73 M. F. Qiao, N. Y. Ji, F. P. Miao and X. L. Yin, *Magn. Reson. Chem.*, 2011, **49**, 366–369.

74 S. C. Mao, D. Q. Liu, X. Q. Yu and X. P. Lai, *Biochem. Syst. Ecol.*, 2011, **39**, 253–257.

75 A. D. A. Guerriero, Michele, F. Pietra, O. Ribes and D. Duhet, *Helv. Chim. Acta*, 1988, **71**, 1094–1100.

76 V. Di Marzo, M. Ventriglia, E. Mollo, M. Mosca and G. Cimino, *Experientia*, 1996, **52**, 834–838.

77 N. M. R. Carballeira, D. Elba, A. Sostre, A. D. Rodriguez, J. L. Rodriguez and F. A. Gonzalez, *J. Nat. Prod.*, 1997, **60**, 502–504.



78 T. Yamashita, Y. Nakao, S. Matsunaga, T. Oikawa, Y. Imahara and N. Fusetani, *Bioorg. Med. Chem.*, 2009, **17**, 2181–2184.

79 A. Guerriero, M. D'Ambrosio, V. Cuomo, F. Vanzanella and F. Pietra, *Helv. Chim. Acta*, 1989, **72**, 438–446.

80 A. Guerriero, M. D'Ambrosio, V. Cuomo, F. Vanzanella and F. Pietra, *Helv. Chim. Acta*, 1988, **71**, 57–61.

81 K. Trisuwant, V. Rukachaisirikul, S. Phongpaichit, S. Preedanon and J. Sakayaroj, *Arch. Pharmacal Res.*, 2011, **34**, 709–714.

82 L. Calcul, C. Waterman, W. S. Ma, M. D. Lebar, C. Harter, T. Mutka, L. Morton, P. Maignan, A. Van Olphen, D. E. Kyle, L. Vrijmoed, K. L. Pang, C. Pearce and B. J. Baker, *Mar. Drugs*, 2013, **11**, 5036–5050.

83 T. K. M. Shing, K. H. Gibson, J. R. Wiley and I. F. Watt, *Tetrahedron Lett.*, 1994, **35**, 1067–1070.

84 B. H. Maskrey, G. W. Taylor and A. F. Rowley, *J. Exp. Biol.*, 2006, **209**, 558–566.

85 K. Gustafson, M. Roman and W. Fenical, *J. Am. Chem. Soc.*, 1989, **111**, 7519–7524.

86 M. A. M. Mondol, J. H. Kim, M. A. Lee, F. S. Tareq, H. S. Lee, Y. J. Lee and H. J. Shin, *J. Nat. Prod.*, 2011, **74**, 1606–1612.

87 M. A. M. T. Mondol, F. Shahidullah, Ji H. Kim, M. ah Lee, H.-S. Lee, Y.-J. Lee, J. S. Lee and H. J. Shin, *J. Nat. Prod.*, 2011, **74**, 2582–2587.

88 M. A. M. Mondol, F. S. Tareq, J. H. Kim, M. A. Lee, H. S. Lee, J. S. Lee, Y. J. Lee and H. J. Shin, *J. Antibiot.*, 2013, **66**, 89–95.

89 X. Xie, D. Meesapyodsuk and X. Qiu, *Appl. Microbiol. Biotechnol.*, 2018, **102**, 847–856.

90 K. T. Peng, C. N. Zheng, J. Xue, X. Y. Chen, W. D. Yang, J. S. Liu, W. B. Bai and H. Y. Li, *J. Agric. Food Chem.*, 2014, **62**, 8773–8776.

91 Q. H. Zhang, C. H. You, F. Liu, W. D. Zhu, S. Q. Wang, D. Z. Xie, O. Monroig, D. R. Tocher and Y. Y. Li, *Lipids*, 2016, **51**, 1051–1063.

92 M. Vagner and E. Santigosa, *Aquaculture*, 2011, **315**, 131–143.

93 R. Vaezi, J. A. Napier and O. Sayanova, *Mar. Drugs*, 2013, **11**, 5116–5129.

94 N. T. Carballeira, E. Janice, E. Ayanoglu and C. Djerassi, *J. Org. Chem.*, 1986, **51**, 2751–2756.

95 F. Shahidi, *Advances in Seafood Byproducts, 2002 Conference Proceedings*, 2003, pp. 247–263.

96 T.-T. Li, Ai-Jun, Y.-Y. Liu, Zi-R. Huang, Xu-Z. Wan, Yu-Y. Pan, R.-B. Jia, B. Liu, X.-H. Chen and C. Zhao, *Food Chem. Toxicol.*, 2019, 131.

97 M. Wolters, J. Ahrens, M. Romani-Perez, C. Watkins, Y. Sanz, A. Benitez-Paez, C. Stanton and K. Gunther, *Clinical nutrition*, Edinburgh, Scotland, 2018, DOI: 10.1016/j.clnu.2018.12.024.

98 J. Bellenger, S. Bellenger, Q. Escoula, C. Bidu and M. Narce, *Biochimie*, 2019, **159**, 66–71.

99 L. Costantini, R. Molinari, B. Farinon and N. Merendino, *Int. J. Mol. Sci.*, 2017, **18**, 18.

100 L. L. Ilag, *Medicines*, Basel, Switzerland, 2018, vol. 5.

101 E. Tvrzicka, L. S. Kremmyda, B. Stankova and A. Zak, *Biomed. Pap.*, 2011, **155**, 117–130.

102 E. Kostetsky, N. Chopenko, M. Barkina, P. Velansky and N. Sanina, *Mar. Drugs*, 2018, **16**.

103 S. H. Jonasdottir, *Mar. Drugs*, 2019, 17.

104 R. B. S. S. Nogueira, A. C. A. Tomaz, D. R. Pessoa, A. L. Xavier, J. C. L. R. Pita, M. V. Sobral, M. L. C. Pontes, H. L. F. Pessoa, M. F. F. M. Diniz, G. E. C. Miranda, M. A. R. Vieira, M. O. M. Marques, M. D. V. Souza and E. V. L. Cunha, *Mar. Drugs*, 2017, **15**.

