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Review

High-value compounds from the molluscs of marine and estuarine ecosystems as prospective functional food ingredients: An overview

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ABSTRACT

Extensive biodiversity and availability of marine and estuarine molluscs, along with their their wide-range of utilities as food and nutraceutical resources developed keen attention of the food technologists and dieticians, particularly during the recent years. The current review comprehensively summarized the nutritional qualities, functional food attributes, and bioactive properties of these organisms. Among the phylum mollusca, Cephalopoda, Bivalvia, and Gastropoda were mostly reported for their nutraceutical applications and bioactive properties. The online search tools, like Scifinder/Science Direct/PubMed/Google Scholar/MarinLit database and marine natural product reports (1984–2019) were used to comprehend the information about the molluscs. More than 1334 secondary metabolites were reported from marine molluscs between the periods from 1984 to 2019. Among various classes of specialized metabolites, terpenes were occupied by 55% in gastropods, whereas sterols occupied 41% in bivalves. The marketed nutraceuticals, such as Cadalmin™ green mussel extract (*Perna viridis*) and Lyprinol® (*Perna canaliculus*) were endowed with potential anti-inflammatory activities, and were used against arthritis. Molluscan-derived therapeutics, for example, ziconotide was used as an analgesic, and elisidepsin was used in the treatment of cancer. Greater numbers of granted patents (30%) during 2016–2019 recognized the increasing importance of bioactive compounds from molluscs. Consumption of molluscs as daily diets could be helpful in the enhancement of immunity, and reduce the risk of several ailments. The present review comprehended the high value compounds and functional food ingredients from marine and estuarine molluscs.

1. Introduction

Molluscs comprise a significant share of seafoods (mussels, squids, clams, octopuses, snails), which were used as a balanced protein resource (Haszprunar & Wanninger, 2012). For centuries, the molluscs were provided with extensive range of human resources, such as dyes, shells, ornaments, and currencies other than their nutritive values (Herbert, Hamer, Mander, Mkhize, & Prins, 2003; Joy & Chakraborty, 2017a). For example, “Tyrian purple” made from the secretions of hypobranchial gland of marine muricid snails were considered as major economic factors, among the Roman and Phoenician Empires (Haszprunar & Wanninger, 2012). Over the past decades, the significance of the marine and estuarine molluscs was greatly extended as alternate resources to traditional fishery, among various locations of the world (Saba, 2011). Also, these were found to be the most sought after food in the world, among the coastal populations of developing and underdeveloped countries, like Asia and Africa (Saba, 2011). For example, the green mussel *Perna viridis* was reported as an integral part of the local cuisines, along the Arabian coast of Indian sub-continent (Chakraborty, Chakkalakal, Joseph, Asokan, & Vijayan, 2016). In several ancient cultures, the molluscs were regarded not only as a healthy diet, but also they were featured in a wider range of traditional remedies (Herbert et al., 2003). For instance, the internal shells of cephalopod, *Spirula spirula* was the most expensive marine mollusc in the traditional medicine market of the Durban city in South Africa (Herbert et al., 2003). Thus, the marine and estuarine habitats were prominently contributed towards the development of prospective therapeutic leads, functional foods, nutraceutical and pharmaceutical preparations. The organisms belonging to the class of *Mollusca* are of special interest, and they were widely distributed in the marine and estuarine ecosystems (Fig. 1). A total of seven classes of molluscs were classified, which includes Monoplacophora, Aplacophora, Polyplacophora, Bivalvia,

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Fig. 1. Representative photographs of molluscs (collected from the southwest coastal waters of India) belonging to the classes of gastropods (**A**) *Babylonia spirata* (collected from the harbors of Neendakara, Kerala) cephalopods (**B**) *Uroteuthis (Photololigo) duvauceli* (collected from the harbors of Thoppumpadi, Kerala), and bivalves (**C**) *Perna viridis* (collected from Elathur, Calicut, Kerala), (**D**) *Paphia malabarica* (collected from the Ashtamudi Lake, Kerala), (**E**) *Crassostrea madrasensis* (collected from the Sathara Island, Cochin, Kerala), (**F**) *Villorita cyprinodes* (collected from the Vembanad Lake, Kerala).

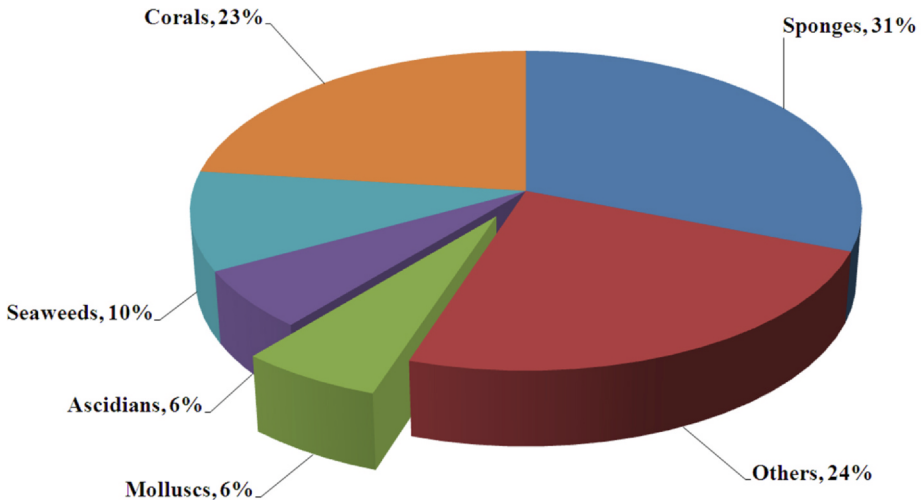


Fig. 2. Percentage share of molluscs among various classes of marine organisms.

Scaphopoda, Gastropoda, and Cephalopoda based upon their phylogenetic analysis (Haszprunar & Wanninger, 2012) (Description S1; Figs. S1-S2). The percentage distributions of prominent groups of marine organisms against molluscs (6%) were plotted in Fig. 2.

Marine and estuarine ecosystems are extremely complex with wide-ranging pressure limits from 1 to 1000 atm, nutrient limits (oligotrophic or eutrophic), thermal conditions from freezing point in Antarctic to 350 °C in the deep hydrothermal regions (Costa-Lotufo, Wilke, Jimenez, & Epifanio, 2009). Chemically or structurally distinctive bio-potent secondary metabolites were originated through their varied biosynthetic mechanisms as a part of their defensive mechanisms to survive against the extreme stress factors in the marine ecosystems (Costa-Lotufo et al., 2009), which could not be found in any terrestrial organisms. These secondary metabolites were regarded as the chemical weapons to withstand in their unfavourable environmental conditions. Although, scattered reports were available to substantiate the health benefits, and therapeutic pluralities of the molluscs. The trends in the publications and patents were found to be gradually increasing in the recent times, which showed the greater interest of the researchers in this area (Ahmad, Liu, Kotiw, & Benkendorff, 2018; Benkendorff, 2018; Blunt et al., 2018; Carroll et al., 2019; Moodie, Sepčić, Turk, FrangeŽ, & Svenson, 2019). Molluscs of marine and estuarine origin were considered as the vital part of the traditional medicine, which were used as prospective sources of medicinally important products for many cultures around the world (Khan & Liu, 2019) (Description S2; Table S1). The biological activities and secondary metabolites described from the molluscan extracts also found to be increased (Cimino & Gavagnin, 2006). Molluscs were accounted for substantial emphasis in the exploration for biologically active metabolites, with more than 1,145 compounds in the past few decades (Benkendorff et al., 2015). Around 52% of the natural compounds identified from molluscan origin were not analyzed for any kind of biological activities, whereas lesser than

1% of identified molluscan species were studied for the presence of bioactive secondary metabolites (Ahmad et al., 2018). More recently, the molluscan natural products, and their synthetically formulated structural analogs were recognized in the clinical trials of various diseases (Simmons, Andrianasolo, McPhail, Flatt, & Gerwick, 2005). For instance, the molluscan derived natural product, ziconotide have completed the clinical trials and sanctioned by the Food and Drugs Administration (FDA) for medication of severe pain (Mayer et al., 2010). Therefore, the rich diversity of molluscan species belonging to the marine and estuarine origin represents an unexploited resource of bioactive compounds to formulate high value compounds and therapeutic leads (McClintock & Baker, 2001). Recently, there is a substantial exploitation of molluscan derived compounds as pharmaceuticals and functional food supplements (McClintock & Baker, 2001).

The present review article extensively comprehended the health benefits, commercial significance, nutritive values, pharmacological potentials, secondary metabolites, biochemical classification of secondary metabolites, nutraceuticals, pharmaceutically prospective lead drugs supported by the list of publications and patents. This extensive review on the molluscan phylum would help in the future research activities, particularly in the development of functional foods, nutraceuticals, and therapeutic leads with multi-targeted bioactivities.

2. Materials and methods

The review was carried out through extensive literature search, using electronic databases, and online search tools, such as Scifinder, Science Direct, PubMed, Google Scholar and MarinLit database. We have reviewed a total of about 479 articles to collect all the information with regard to molluscs, including the annual review papers titled as marine natural product reports between the periods 1984 to 2019 (Blunt et al., 2007, 2009, 2018, Blunt, Copp, Keyzers, Munro, & Prinsep, 2012, 2013, 2014, 2015, 2016, 2017, Blunt, Copp, Munro, Northcote, & Prinsep, 2003, 2004, 2005, 2006, 2008, 2010, 2011; Carroll et al., 2019; Faulkner, 1984, 1986, 1987, 1988, 1990, 1991, 1992, 1993, 1994, 1995, 1997, 1998, 2000, 2002). The keywords "molluscs or molluscan" in MarinLit were used to summarize the published literatures on natural products reported from the molluscs. In SciFinder, the separate keywords, such as "bivalves", "cephalopods", and "gastropods" retrieved the detailed information about the molluscs. Keywords like "ω-conotoxin MVIIA", SNX-111", "ziconotide", "prialt" "elisidepsin", "kahalalides", "zalypsis", "jorumycin", "dolastatins", "dolastatin 10", "dolastatin 15", "LU-103793", "cematodin, ILX651", "synthadotin", "kulokekahilide-2", "aurilide", "spisulosine ES-285", "keenamide A" were used in the PubMed search to obtain the details on the bioactive compounds and their applications. The search was carried out using the terms "antioxidant", "anti-inflammatory", "antihypertensive", "antidiabetic", "antimicrobial", "antiviral", "anticancer", "nutraceuticals", "functional foods", "fatty acids", "macrolides", "peptides", "polypropionates", "alkaloids", "sterols", and "terpenes" in combination with "bivalves", "cephalopods", and "gastropods" in Google search, Scifinder, and Science Direct, to obtain the reports of literature on the pharmacological activities and bioactive compounds of molluscs. Some selected species namely, "*Haliotis diversicolor*", "*Haliotis discus*", "*Babylonia spirata*", "*Babylonia zeylanica*", "*Bursa spinosa*", "*Chicoreus ramosus*", "*Paphia malabarica*", "*Villorita cyprinoides*", "*Meretrix meretrix*", "*Perna viridis*", "*Perna canaliculus*", "*Crassostrea madrasensis*", "*Uroteuthis* (*Photololigo*) *duvauceli*", "*Cistopus indicus*", "*Sepia pharaonis*", "*Sepiella inermis*", "*Amphioctopus marginatus*" were reviewed in Google search. The searches of granted patents on molluscs were retrieved from Google patents. Unpublished papers and papers in non-English languages were considered as exclusion criteria. The latest date of literature searches was on 23rd October 2019. After reviewing the full paper, about 479 articles were regarded as potentially suitable publications for inclusion.

3. Commercial significance of molluscs of marine and estuarine origin

The shares of the 104 aquaculture molluscan species (16.1 million metric tons) were estimated at US$ 19 billion (FAO, 2016). In 2014, the production of aquatic animals were recorded to 73.8 million tons, with assessed first-sale cost of US$ 160.2 billion, in which the second largest class was found to be the molluscs with 16.1 million tons with an estimated value of US$ 19 billion (FAO, 2016). However, the global marine and estuarine molluscan production in 2016 was increased to 17.1 million tons with estimated first-sale cost of USD 29.2 billion (FAO, 2018). According to FAO, 2020, the global production of molluscs, in particular, bivalves were found to be 17.7 million tonnes. The cephalopod species plays an important role in the exploited fisheries sectors all over the world, and began to receive more interest due to the cumulative export demands (Okuzumi & Fujii, 2000). This might be due to the enhanced alertness about their dietary potentials (Okuzumi & Fujii, 2000). Deteriorating catches of ground fishes have tempted to practice the potential non-traditional cephalopod species. During the last forty years, cephalopod stockings were increased from 1 million metric tons (1970) to 4 million metric tons (2010), whereas the share of squids, cuttlefishes and octopuses in world's fish market were increased to 4% (2010) with greater market price. Molluscan fishery in the Asian continent was largely comprised of squids (*U. duvauceli*, *Doryteuthis sibogae*), scallop (*Patinopecten yessoensis*) and cuttlefish (*Sepia aculeata*, *S. pharaonis*, *Sepia elliptica*, *Sepia officinalis*) (FAO, 2016). Among the gastropods, abalone aquacultures were mainly found in China, and it was increased to five times in the recent years (Suleria, Addepalli, Masci, Gobe, & Osborne, 2017). Notably, the molluscan aquaculture, particularly with reference to *Ruditapes philippinarum* (clam), *P. yessoensis* (scallop), *Mytilus edulis* (mussel), *P. viridis* (Asian green mussel), *P. canaliculus* (New Zealand green-lipped mussel) and *Anadara granosa* (clam) (Kim & Venkatesan, 2015), were gained momentum during the recent years. The availability of seafood in 2014 was amounted to 167.2 million metric tons (MMT), out of which the cephalopods alone were accounted for 4.3 MMT (FAO, 2016). Among various cephalopods, *Illex argentines* and *Dosidicus gigas* were accounted for most marketed squids, whereas cuttlefish (300,000 tons) and octopus (350,000 tons) were found to be steady since 2008 (FAO, 2016). After continuous growth, which started during the year of 2008, the cephalopod catches were found to be stable through 2015, but thereafter, exhibited a decreasing trend (Khan & Liu, 2019). China, Peru and India were the major exporters of cuttlefish and squid, whilst China and Morocco were for octopus. The United States, Spain, Japan, Korea, Italy and Hawaii were the major consumers of cephalopods, whereas China and Thailand were the largest importers (Khan & Liu, 2019). The production of squid was found to be higher than 77%, followed by octopus (11%) and cuttlefish (11%) in 2016 (FAO, 2018). Among bivalve molluscs, mussels, clams, scallops and oysters dominated as highly traded markets and farmed species. China was found to export bivalves three times as much as Chile, in 2016 (Wijsman, Troost, Fang, & Roncarati, 2019), whereas the former has significant domestic consumption, and produces more than 85% of the world and European Union having the largest market for bivalves (Wijsman et al., 2019). Globally, the bivalve production for human consumption was greater than 15 million tons per year (2010–2015), which was found to be 14% of the total marine production in world. More than 85% of bivalve production was reported from the aquaculture, and only 11% was acquired from the wild conditions (Wijsman et al., 2019). Production of oyster was found to be higher of about 54%, followed by scallops (11%), mussels (18%) and clams (4%) in 2016 (FAO, 2018). The cupped oysters, *Crassostrea* spp. were found to be the major molluscan species (total of 28%), followed by clam, *R. philippinarum* (total of 25%), scallops, Pectinidae (total of 11%) and other molluscs (total of 11%), according to the world's aquaculture report (Fig. 3) (FAO, 2018). Ten major cultured molluscs were compared in Table 1, according to their value and production in 2015, in

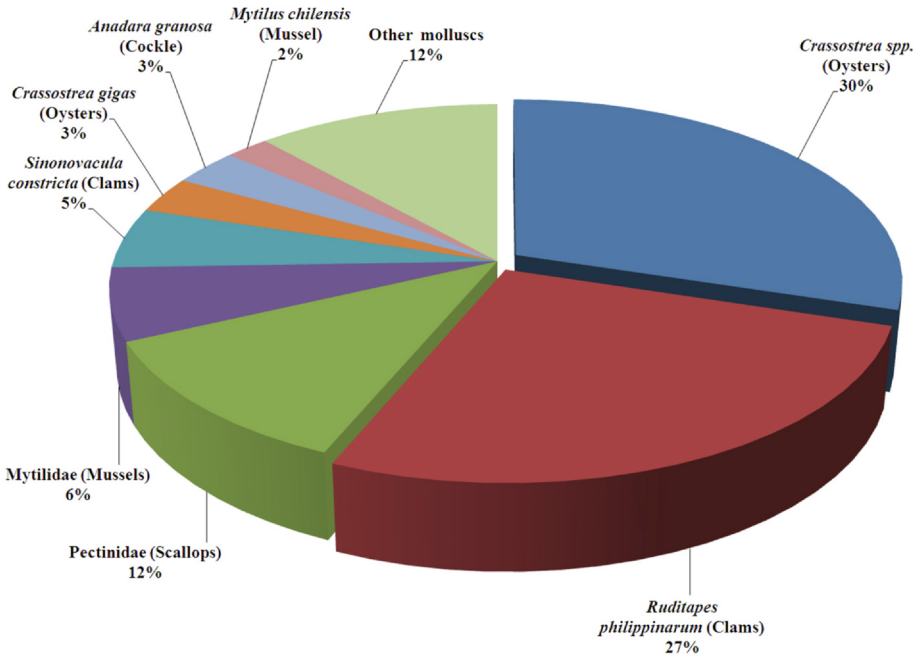


Fig. 3. Percentage share of the major molluscan species produced in world aquaculture (FAO, 2018).

Table 1
Comparison of ten major cultured molluscan species by their value and production in 2015 according to FAO, 2017

Species	Production (tons)	Value (million USD)
Crassostrea gigas	5,178,707	3880.89
Ruditapes philippinarum	4,049,540	3708.93
Sinonovacula constricta	793,708	714.34
Anadara granosa	441,303	576.82
Patinopecten yessoensis	251,907	475.15
Mytilus chilensis	208,707	1711.4
Mytilus edulis	192,271	325.05
Perna canaliculus	76,811	494.86
Meretrix lusoria	64,060	141.03
Argopecten purpuratus	25,988	217.97

which, *C. gigas* recorded a higher value of 3880.89 million USD and 5,178,707 tons production (FAO, 2017). The inland aquaculture production of molluscs was higher for Asia, which was found to be 286 thousand tons of live weight, whereas there was no record of Inland molluscan aquaculture in the countries like Africa, America, Europe, and Oceania (FAO, 2018). Marine and coastal aquaculture of molluscs were also higher for Asia of about 15,550 thousand tons of live weight, followed by those in Africa (6 thousand tons), America (574 thousand tons), Europe (613 thousand tons) and Oceania (112 thousand tons), in descending order (FAO, 2018). According to FAO 2016, the highest producer of molluscs was China with a production of 13418.7 thousand tons followed by Japan (376.8 thousand tons) and Korea (359.3 thousand tons), in descending order. Bivalves were promoted as sustainable food items, and therefore, the demand has been increased during the recent years (FAO, 2018). Estimated annual landings of mussels, oysters and clams in India during 2015 were 92,513 tons (CMFRI, 2015–2016), and therefore, were found as valuable fishery resources in various parts of the coastal regions of the penninsular India. The distribution and availability of major molluscan species, such as *P. viridis*, *P. canaliculus*, *P. malabarica*, *H. discus*, *M. edulis*, *S. pharaonis*, and *A. marginatus* around the world were depicted in Fig. S3 (retrieved from www.discoverlife.org, accessed on 12/10/2019).

4. Health benefits and nutritive values of molluscs of estuarine and marine origin

Studies on the health benefits and nutritive values of estuarine and marine molluscs as food and food supplements were interestingly increased in the last few years. Molluscs were found to play a significant role in water filtration, recycling of nutrients, soil-generation, and as bio-indicators of the environmental quality in all the aquatic habitats (Avila, Iken, Fontana, & Cimino, 2000). Rich and significant nutrient contents in the molluscs were reported to play prominent roles in the enhancement of immune systems in our body (Khan & Liu, 2019). The dietetic composition of major molluscs, such as abalone, snail, mussel, oyster, scallop, clam, octopus, squid and cuttlefish were tabulated in Table 2 (accessed on 10/10/2019) (USDA, 2019a-2019i). Also, the saturated (SFA), mono-unsaturated (MUFA), and polyunsaturated (PUFA) fatty acids, along with docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) contents of the above mentioned molluscs were compared (Fig. 4) (USDA, 2019a-2019j). These data suggested that the PUFA and EPA contents were higher in oysters, followed by those in mussels and squid. PUFAs were found to be the key biochemical markers of cephalopods, whereas DHA and EPA were found to be vital for various human metabolic and physiological functions (Simopoulos, 2009). Long chain *n*-3 PUFAs were found to be essential to reduce the risk of numerous health problems, such as cardiovascular illnesses, type-2 diabetes, hypertension, inflammation, asthma and cancer (Simopoulos, 2009). The Asian communities consume molluscan species of marine and estuarine origin due to their health-promoting pluralities (Kim & Pallela, 2012). It was reported that some of the molluscan bioactivities and nutritive factors were retained even after the pre-treatments and cooking (Su & Liu, 2013).

Cephalopods were found to be rich in protein, and 80% of their total fleshy material was considered to be edible for human consumption (Chakraborty et al., 2016). The edible portions of these species were accounted for *n* , minerals, vitamins along with essential amino acids including antioxidative selenium (Zlatanos, Laskaridis, Feist, & Sagredos, 2006). Several reports were available on the biological description, occurrence, proximate composition, and nutritional qualities of the cephalopod species (Okuzumi & Fujii, 2000; Pierce et al., 2008). Compositions of fatty acid profiles and its relation to seasonal or annual

Table 2
Dietetic composition of major molluscs based on United States department of agriculture (USDA), 2019

Mollusc	Abalone[a]	Snail[b]	Mussel[c]	Oyster[d]	Scallop[e]	Clam[f]	Octopus[g]	Squid[h]	Cuttlefish[i]
Protein (g)	17.1	16.1	11.9	9.5	12.1	14.7	14.9	15.6	16.2
Lipid (g)	0.8	1.4	2.2	2.3	0.5	1.0	1.0	1.4	0.7
Calcium (mg)	31.0	10.0	26.0	8.0	6.0	39.0	53.0	32.0	90.0
Iron (mg)	3.19	3.5	3.9	5.1	0.4	1.6	5.3	0.7	6.0
Magnesium (mg)	48.0	250.0	34.0	22.0	22.0	19.0	30.0	33.0	30.0
Phosphorus (mg)	190.0	272.0	197.0	162.0	334.0	198.0	186.0	221.0	387.0
Potassium (mg)	250.0	382.0	320.0	168.0	205.0	46.0	350.0	246.0	354.0
Sodium (mg)	301.0	70.0	286.0	106.0	392.0	601.0	230.0	44.0	372.0
Zinc (mg)	0.82	1.0	1.6	16.6	0.9	0.5	1.7	1.5	1.7
Copper (mg)	0.2	0.4	0.09	1.6	0.02	0.1	0.4	1.9	0.6
Manganese (mg)	0.04	0	3.4	0.6	0.02	0.1	0.03	0.03	0.1
Selenium (μg)	44.8	27.4	44.8	77.0	12.8	30.6	44.8	44.8	44.8
Vitamin C (mg)	2.0	0	8.0	8.0	0.0	0	5.0	4.7	5.3
Vitamin A, Retinol Activity Equivalent (μg)	2.0	30.0	48.0	81.0	1.0	90.0	45.0	10.0	113.0
Vitamin E (mg)	4.0	5	0.55	0	0	0.7	1.2	1.2	0
Vitamin D (IU)	0.0	0	0.0	1.0	1.0	1.0	0	0	0
Vitamin K (μg)	23.0	0.1	0.1	0	0	0.2	0.1	0	0
Cholesterol (mg)	85.0	50.0	28.0	50.0	24.0	30.0	48.0	233.0	112.0

[a] USDA, 2019a; [b]USDA, 2019b; [c]USDA, 2019c; [d]USDA, 2019d; [e]USDA, 2019e; [f]USDA, 2019f; [g]USDA, 2019g; [h]USDA, 2019h; [i]USDA, 2019i.

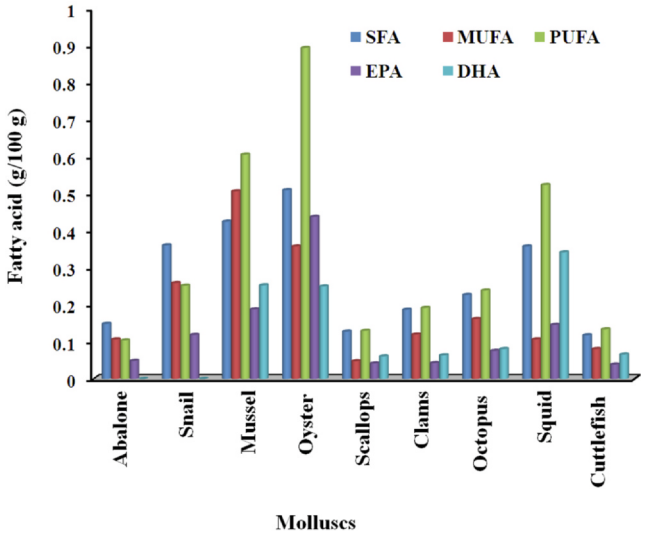


Fig. 4. Saturated (SFA), monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids along with docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) contents of major molluscs, such as abalone, snail, mussel, oyster, scallop, clam, octopus, squid and cuttle fish based on the statistics of the United States Department of Agriculture (USDA), 2019 (accessed on 10/10/2019) (USDA, 2019a; 2019b; 2019c; 2019d; 2019e; 2019f; 2019g; 2019h; 2019i).

variations of cephalopods were previously studied (Ozyurt, Duysak, Akamca, & Tureli, 2006). Previous studies of *S. pharaonis*, *A. neglectus* and other species of cuttlefishes, octopuses and squids were reported to exhibit prominent lipid contents (greater than 2 mg/100 g), which were found to be lesser than marine fishes (Chakraborty et al., 2016; Zlatanos et al., 2006). Edible portions of cephalopod species, *U. duvauceli*, *S. inermis*, *S. pharaonis*, *C. indicus*, and *A. neglectus* were reported for greater contents of PUFAs (Table 3) (Chakraborty et al., 2016; Ozyurt, Duysak, Akamca, & Tureli, 2006). The previous studies described that the cephalopods were found to be rich in protein, EPA, DHA, micro/macro minerals, vitamins, amino acids, and therefore, these species could be regarded as an effective health food for human consumption (Chakraborty et al., 2016). Previous studies of edible molluscs, such as Indian squid *U.* (*Photololigo*) *duvaucelii*, the veined octopus *A. marginatus*, the spineless cuttlefish *S. inermis*, and the oyster *Crassostrea bilineata* were reported for their greater contents of protein with prominent essential to non-essential amino acid ratios (Krishnan, Chakraborty, & Vijayagopal, 2019). These were also reported for their prominent levels of *n*-3/*n*-6, EPA and DHA fatty acid ratio, which suggested their utilisation as balanced diet (Krishnan et al., 2019).

During the recent years, the gastropods are gaining greater significance among molluscs due to their commercial potentials. Previous studies were reported with greater percentages of proteins in the predator gastropod whelks, when compared to the herbivore gastropods (Zarai et al., 2001). Predatory carnivore gastropods, such as *Chicoreus ramosus* (Ramesh & Ayyakkannu, 1992), *Hexaplex trunculus* (Zarai et al., 2001), *Thais haemastoma* (Belisle & Stickle, 1978) and *Rapana venosa* (Celik et al., 2014) were reported for their higher protein contents. Nutritional profiles of the gastropods were found to vary according to the type of organisms, body parts, seasonal changes, collection sites, spatial changes, temporal variations, and reproductive cycles (Smoothey, 2013). The lipid content was found to be lesser in the predatory gastropods than those in the herbivorous ones (Belisle & Stickle, 1978; Ramesh & Ayyakkannu, 1992). The visceral lipid content was greater when compared to the foot tissues, and the visceral tissues were considered as the lipid storing part of the gastropods. Usually, visceral tissues in the larger gastropods were not recommended for consumption, and the foot tissues were typically consumed by the people (Saito & Aono, 2014). Therefore, the previous studies concluded that the foot tissues were suitable for human diet, due to higher protein and lesser lipid contents (Lah et al., 2016). The fatty acid composition, especially PUFA contents along with DHA and EPA were previously reported in the various gastropods, particularly in the snails (Brazao et al., 2003; Lah et al., 2016). Gastropods were found to possess various minerals, such as potassium, sodium, selenium, zinc, iron, and sulfur (Lah et al., 2016). Also, the essential amino acid components were considerably higher in the gastropods, such as *Chicoreus virginineus*, *Phalium glaucum*, *Rapana rapiformis*, and *Tonna dolium* (Babu, Venkatesan, & Rajagopal, 2011). The branched murex, *C. ramosus* from Gulf of Mannar was studied for their nutritive values, and the studies suggested that these low-valued gastropod species could be considered as valuable depot of essential nutritional elements, functional foods, and as a health food for human consumption (Salas et al., 2018). It exhibited lesser sodium/potassium ratio with greater contents of calcium, phosphorus, and antioxidative mineral, selenium. Therefore, *C. ramosus* could be utilized to reduce the risk of hypertension, and cardiovascular diseases along with higher bone mineralization (Salas et al., 2018). These studies described the nutritional qualities of gastropods, and suggested that these could contribute towards the people's diets, as nutritional health food, particularly in the developing countries.

Bivalve molluscs are prominent seafoods at the coastline regions,

Table 3
Nutritional profiling of major species of molluscs

Nutritional parameters	Bivalves				Cephalopods						Gastropods
	[a]*Paphia malabarica*	[a]*Villorita cyprinoides*	[b]*Crassostrea bilineata*	[c]*Perna viridis*	[b]*Amphioctopus marginatus*	[d]*Amphioctopus neglectus*	[d]*Cistopus indicus*	[d]*Uroteuthis duvauceli*	[d]*Sepia pharaonis*	[d]*Sepia inermis*	[e]*Chicoreus ramosus*
Lipid (g/100 g)	1.77	2.27	1.19	1.47	*1.58	*2.50	*1.75	*1.75	*2.56	*1.30	0.39
Cholesterol (mg/100 g)	59.02	56.27	34.74	96.6	99.43	103.65	128.64	191.65	320.15	307.51	28.7
True protein (mg/100 g)	#12.64	#11.15	$18.36	7.14	$13.54	1202.74	1850.21	1951.39	1449.03	1874.2	#12.89
Macronutrients (mg/100 g)											
Na	118.50	92.00	16.57	1967.25	§7.65	172.45	170.14	171.98	170.18	172.77	95.00
K	94.23	60.21	§48.25	1450.50	§20.05	144.56	184.83	176.13	201.2	134.67	149.6
Ca	34.25	28.52	§17.92	287	§13.32	73.72	54.04	72.82	108.41	79.73	38.10
P	583.62	534.23	92.71	ND	§83.72	86.07	66.33	85.63	80.40	72.37	98.00
Mg	36.75	25.86	16.54	64.33	§12.55	92.83	104.78	127.36	127.28	109.76	75.79
Micronutrients (mg/100 g)											
Mn	2.03	1.75	§1.38	ND	§0.04	6.39	6.51	6.57	6.92	6.43	0.11
Cu	0.46	0.30	§0.86	0.05	§0.26	3.55	7.54	1.33	5.57	5.33	0.16
Zn	3.01	3.26	§4.99	1.55	§1.06	13.08	14.17	7.21	15.18	8.34	1.27
Fe	7.64	5.65	§2.44	6.10	§2.21	7.44	6.60	10.42	7.79	8.45	1.65
Se (μg/100 g)	30.15	27.27	§0.02	0.04	§0.06	9.31	9.45	9.54	8.95	9.34	30.44
Vitamins											
Retinol A (IU)	39.46	41.11	8.09	11.89	99.42	15.35	8.39	26.51	21.6	54.81	€21.89
Cholecalciferol D3 (IU)	161.29	183.28	489.20	410.00	93.68	4.39	3.30	1.61	3.51	1.52	€1.21
α-tocopherol E (IU)	0.39	0.32	0.21	0.15	16.61	11.43	3.54	1.45	5.29	11.26	€55.82
Phylloquinone K1 (μg/100 g)	0.75	0.65	1.84	2.72	1.48	0.01	1.58	0.01	0.26	ND	ND
Ascorbic acid C (IU)	10.20	11.36	€48.36	12.14	€42.62	2.20	1.80	2.90	0.70	2.80	€45.45
Fatty acid (% total fatty acids)											
Total SFA	33.84	47.77	43.01	39.56	35.85	*879.25	*461.62	*591.00	*720.19	*398.26	29.14
Total MUFA	23.15	25.57	26.79	21.63	29.18	*477.06	*485.54	*180.95	*515.28	*166.29	20.94
EPA	7.68	3.57	7.57	7.95	8.29	*238.84	*135.57	*213.54	*360.96	*119.25	15.83
DHA	14.35	3.22	8.68	9.60	14.70	*645.05	*374.68	*534.89	*599.90	*267.63	17.17
Total PUFA	34.33	18.46	26.35	25.38	31.44	*1076.25	*660.86	*845.78	*1211.27	*594.9	49.77
Amino acids (mg/100 g)											
Histidine	14.64	13.54	ND	38.1	10.00	12.30	16.01	6.57	4.31	3.19	69.30
Methionine	16.67	18.32	90.00	25.81	50.00	22.10	7.35	4.41	2.15	1.32	106.20
Valine	29.47	30.57	150.00	59.95	10.00	28.37	12.09	6.18	3.43	2.62	112.90
Threonine	27.23	29.95	120.00	61.40	70.00	30.15	12.18	6.48	4.27	2.11	186.30
Isoleucine	29.62	31.12	140.00	52.21	60.00	33.12	13.05	7.21	3.47	2.44	130.00
Leucine	42.95	48.35	220.00	116.30	90.00	46.57	19.28	11.39	5.07	3.11	321.60
Lysine	43.57	41.67	160.00	91.30	140.00	36.26	19.11	12.51	4.07	3.37	263.00
Phenylalanine	28.20	33.11	110.00	63.63	90.00	34.19	9.14	5.25	3.10	2.25	117.30
Total AA	551.78	566.12	2620.00	1578.77	1530.00	561.50	270.03	142.18	74.63	47.35	3836.50
Total EAA	285.29	300.20	1340.00	679.53	870.00	316.19	141.44	75.11	39.28	26.48	1857.90
Total NEAA	266.49	265.92	1280.00	899.24	660.00	245.31	128.59	67.07	35.35	20.87	1978.60

SFA – Saturated fatty acid; MUFA – Monounsaturated fatty acid; PUFA – Polyunsaturated fatty acid; AA – Amino acid; EAA – Essential amino acid; NEAA – non-essential amino acid. *mg/100 g; #mg/g; $g/100 g; §mg/kg; μg/100 g.

[a] Joy and Chakraborty, 2017a.
[b] Krishnan, Chakraborty, & Joy, 2019.
[c] Chakraborty, Chakkalakal, & Joseph, 2016.
[d] Chakraborty et al., 2016.
[e] Salas, Chakraborty, Sarada, & Vijayagopal, 2018.

and were found to constitute a dominant share in the global trade markets (Chakraborty et al., 2014; Xie et al., 2012). However, these were not comprehensively investigated for their dietary and nutritional potentials. Bivalves were found to be the potential resources of *n*-3 PUFAs, comprising of EPA/DHA (Chakraborty et al., 2014a). Bivalve molluscs were potential sources of anti-inflammatory agents (E and D resolvins), which were found to play prominent roles to combat the biosynthesis of inflammatory prostanoids (Chakraborty, Joseph, & Chakkalakal, 2014b). In general, these species were reported to provide an inexpensive source of proteins, minerals, amino acids, and vitamins (Astorga-Espana, Rodriguez, & Romero, 2007). The bivalves, *Ruditapes decussatus* and *Mytilus galloprovincialis* collected from the Mediterranean Sea were reported to exhibit greater contents of lipid and protein (Saba, 2011). The Asian hard clam, *Meretrix lusoria* and *M. meretrix* displayed prominent nutritional qualities (Karnjanapratum, Benjakul, Kishimura, & Tsai, 2013; Xie et al., 2012), and were considered as low-valued health food items. In view of the nutritional qualities, bivalves were positioned next to the finfish and prawns. Nutritional qualities of green mussels (*P. viridis*) and edible oysters (*C. madrasensis*) were reported previously, and were suggested as the substitutes to equilibrate the

greater consumption of inflammatory *n*-6 fatty acids (Table 3) (Chakraborty et al., 2016; Chakraborty, Chakkalakal, Joseph, & Joy, 2016). The nutritional quality parameters, such as mineral composition, fatty acids, glycogen, cholesterol, vitamins, carotenes, and the commercial quality indicators of *Chamelea gallina* were studied previously (Orban et al., 2006). Proteins, minerals, lipids, glycogen, along with minor components of lipophilic and hydrophilic nature were found to contribute towards the nutritive importance and organoleptic features of clams (Orban et al., 2006). The historical seafood, *M. meretrix* was considered as the valued resources of ancient Chinese therapeutics (Xie et al., 2012). Nutritive values of *P. malabarica and V. cyprinoides* were described by their greater contents of *n*-3 PUFAs (greater than 15% total fatty acids, TFA), EPA (greater than 3% TFA), and DHA (greater than 3% TFA) (Joy & Chakraborty, 2017a). Greater calcium and phosphorus contents (greater than 530 mg/100 g wet tissue), higher vitamin A (greater than 35 IU) and D_3 (greater than 160 IU), along with higher levels of selenium (Se, greater than 25 μg/100 g wet tissue) (Joy & Chakraborty, 2017a), were also reported in these bivalve clams (Table 3). These previous studies established the nutritional importance of marine and estuarine molluscs for use as nutritional health foods, particularly in coastal regions of the world.

5. Nutraceuticals, functional foods and high value compounds from the marine and estuarine molluscs

In the recent days, the concept of nutraceuticals and functional foods were interestingly increased. Nutraceuticals and functional foods became a part of consumer's daily diets, as a preventive healthcare measure against increased life-style diseases (Mordor Intelligence, 2015–2019). The nutraceuticals signified the functionalities of pharmaceuticals in the food itself. Therefore, the food supplements as daily diets could prevent the diseases, and these could lead to the reduced usage of synthetic drugs with severe side effects. The global market of nutraceuticals were valued at around USD 250 billion in 2014, and believed to reach approximately USD 385 billion by 2020, at a CAGR (compound annual growth rate) of 7.5% from 2016 to 2021 (Mordor Intelligence, 2015–2019). Among various marine organisms, molluscs occupied an integral part in the formulation of several nutraceuticals and could be used as functional foods to improve the health benefits (Table 4; Fig. 5). For example, the dried abalone powder was commercialized as a nutraceutical product in New Zealand (Lee, 1993). The

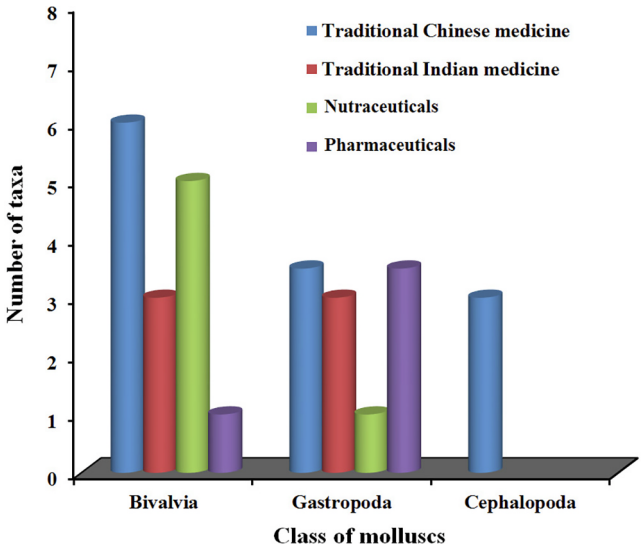


Fig. 5. Numbers of taxa in different classes of molluscs (particularly, gastropods, cephalopods and bivalves) that were reported for their uses in medicinal applications (traditional Chinese medicines, traditional Indian medicines, nutraceuticals and pharmaceuticals) (Benkendorff, 2010). No record of medicinal applications with regard to the molluscan classes, such as Monoplacophora, Scaphopoda, Solenogastres, Caudofoveata and Polyplacophora was available.

nutraceutical product, ABA-Active, an abalone powder from *Haliotis iris* was reported to strengthen the body, enhance the liver function, beneficial to the heart, promotes sexual function, and helps to prevent anemia (Aroma New Zealand, 2019). A nutraceutical supplement was marketed from *P. viridis* (Cadalmin™ Green Mussel extract), which exhibited potent *in vivo* and *in vitro* anti-inflammatory effects against pro-inflammatory prostanoids, was found to be effective against arthritis (Chakraborty et al., 2014).

Anti-inflammatory composition of Cadalmin™ Green Mussel extract from *P. viridis* was marketed as Musseltone®, which demonstrated the potential activities against cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) enzymes (Chakraborty et al., 2014a). Natural remedies of New Zealand green-lipped mussel, *P. canaliculus* were promoted as anti-inflammatory agents to treat the progression of the ailments of

Table 4
Commercialized nutraceutical products reported from different molluscan species

Commercial nutraceutical products	Species	Therapeutic properties	References
Oyster Plus	*Crassostrea* sp. (Oyster)	Improves men's reproductive health, supports immunity, health and vitality	Goodhealth, 2018a
Cadalmin™ Green Mussel extract (GMe)	*Perna viridis* (Green mussel)	Effective in chronic joint pain and arthritis and improves cardiovascular function and inflammatory disorders	Chakraborty, Chakkalakal, & Joseph, 2014
Abalone	*Haliotis* sp. (Snail)	Improves eye health, general health and vitality	Goodhealth, 2018b
ABA-Active, an abalone powder	*Haliotis iris* (Snail)	Strengthens the body, enhance the liver function, beneficial to the heart, promotes sexual function and helps to prevent anemia	Aroma New Zealand Ltd, 2019
Lyprinol®	*Perna canaliculus* (Green-lipped mussel)	Anti-inflammatory activity against cyclooxygenase-2 and 5-lipoxygenase inflammatory enzymes, activities against arthritis and asthma	Whitehouse et al., 1997
Mussel 6000	*Perna canaliculus* (Green-lipped mussel)	Nutritional support for joint stiffness, comfort, lubrication and mobility and overall joint repair	Goodhealth, 2018c
Aquatone	*Perna canaliculus* (Green-lipped mussel)	Effective in retaining healthy joints	Nature's Best, 2018
GlycOmega-PLUS™	Green-shell mussel powder	Reduce joint pain and to enhance joint mobility	Aroma New Zealand Ltd, 2019
Seatone®	*Perna canaliculus* (Green-lipped mussel)	Anti-inflammatory supplement	Cobb & Ernst, 2006
Bioskincare™	*Helix aspersa*	Cosmeceutical, to repair scars, prevent and remove stretch marks and to firm breasts	Bioskincare, 2019
BioLex	*Perna canaliculus* (Green-lipped mussel)	Active against osteoarthritis	Stebbings, Gray, Schneiders, & Sansom, 2017
Biolane™	*Perna canaliculus* (Green-lipped mussel)	Active against arthritis	Cheras et al., 2005

joint and connective tissues, as well as the symptoms of arthritis (Treschow et al., 2007). Also, several novel anti-inflammatory omega-3 PUFAs were identified from the extracts of *P. canaliculus* (Treschow et al., 2007). Commercial freeze-dried extract of *P. canaliculus* was found to down-regulate the inflammatory responses (Bierer & Bui, 2002), whereas its lipid fraction was marketed as Lyprinol®, which demonstrated the potential activities against arthritis (Whitehouse et al., 1997) and asthma (Gibson, 2000; Halpern, 2000). An anti-arthritic nutraceutical from *P. canaliculus* was marketed as Biolane™, and its activities were compared with the standard anti-arthritic agents like chondroitin sulfate, lyprinol, and glucosamine sulfate (Cheras, Stevenson, & Myers, 2005). Biolane™ was reported to exhibit broad-spectrum of activities including inhibition of pro-inflammatory PGE, COX-2, along with anti-platelet aggregation, and fibrinolytic potencies compared to other agents (Cheras et al., 2005). All these studies supported the oral administration of the green lipped mussel extract to control the inflammatory conditions (Cheras et al., 2005). A wide range of nutraceuticals and functional foods have been developed from this species, including mussel extract, that claimed to have five times greater anti-inflammatory properties than the mussel powder (Aroma New Zealand Ltd, 2019). Another product, GlycOmega-PLUS™ (Greenshell™ mussel powder) was produced from the cold-extracted green lipped mussel, which was clinically proved to reduce joint pain, and enhance joint mobility (Aroma New Zealand, 2019). It was proved as rich source of glycosaminoglycans, the significant components of cartilage, and synovial fluids in joints (Aroma New Zealand Ltd, 2019). GlycOmega-Oil™, a Greenshell™ mussel oil was a rich source of DHA and EPA omega-3 fatty acids, along with 30 other essential fatty acids. This product used for treating the joint, respiratory, and cardiovascular diseases, along with maintaining balanced HDL (high-density lipoprotein) and triglyceride levels (Aroma New Zealand Ltd, 2019). The cost of the mussel powder was $AUD 150/kg, $ 1600/kg for the extract and ~$ 16,000/kg for the Lyprinol® (Benkendorff, 2010). An oyster powder developed from the Pacific oyster, *C. gigas* was promoted as a dietary supplement, which was found to be beneficial for maintaining the blood pressure, cardiovascular health, arthritis, skincare, rheumatism, and liver problems (Aroma New Zealand Ltd, 2019). A nutritional supplement, Seatone® developed from *P. canaliculus* was used as an anti-inflammatory functional food product (Cobb & Ernst, 2006). The cowrie shells (Cypraeidae) were incorporated in the Chinese traditional medicines (Hu, 1980), and was patented for use in the dental fillings (Weil & Manshardt, 1992). Mucus of *C. aspersa* was incorporated in the commercially available cosmeceutical, branded under Bioskincare™, which was claimed for its effects on repairing scars, prevent and remove stretch marks, and to firm the breasts (Bioskincare, 2019).

6. Bioactive secondary metabolites from marine and estuarine molluscs

The reports of marine natural products series described more than 1334 secondary metabolites between the periods 1984 to 2019 from molluscs (Blunt et al., 2007, 2009, 2018, Blunt et al., 2012, 2013, 2014, 2015, 2016, 2017, Blunt et al., 2003, 2004, 2005, 2006, 2008, 2010, 2011; Carroll et al., 2019; Faulkner, 1984, 1986, 1987, 1988, 1990, 1991, 1992, 1993, 1994, 1995, 1997, 1998, 2000, 2002) A year-wise comparison of number of secondary metabolites isolated from the molluscs was depicted in Fig. 6. Previous reports of literature described a total number of 948 compounds from the gastropods, 190 from the bivalves, and 24 secondary metabolites from the cephalopods (Avila, 2006; Benkendorff, 2010). These reports suggested that most of the chemical studies and the isolation of bioactive secondary metabolites were more focused on gastropods, followed by bivalves, and cephalopods. Therefore, we have focused to review the bioactive secondary metabolites, particularly from these three prominent classes of molluscs.

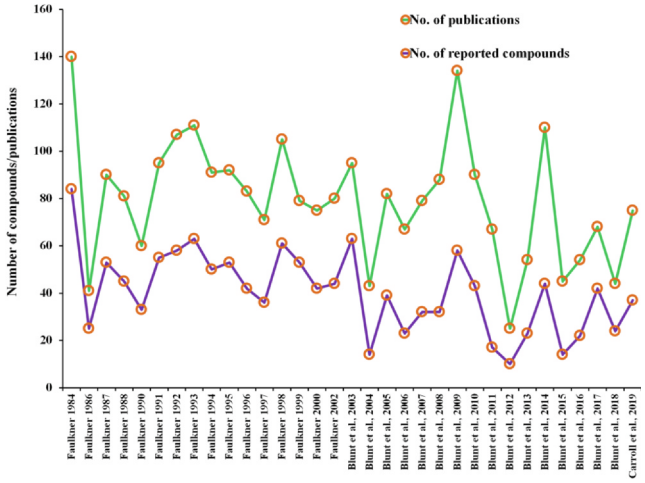


Fig. 6. Aggregate numbers of reported secondary metabolites and papers published (after Faulkner, 1984 to 2002, Blunt et al., 2003 to 2018, Carroll, Copp, Davis, Keyzers, & Prinsep, 2019).

6.1. Cephalopod molluscs

Cephalopods were considered as significant resources of bioactive metabolites with prominent bioactive potentials (Chakraborty & Joy, 2017; Chakraborty et al., 2017). Knowledge of bioactive compounds from these organisms would help to develop newer pharmacophore agents (Chakraborty & Joy, 2017). Even though, limited research works and fewer publications were available on the biologically active molecules from these species, the important cephalopod metabolites were illustrated (Fig. 7, Fig. S4). The pigments, adenochromines **1–3** were reported from *Octopus vulgaris* (Prota, Ito, & Nardi, 1977). Arsenolipids **4–5** were reported from a squid, *Todarodes pacificus* (Ninh, Nagashima, & Shiomi, 2007). Cyclophosphamine extracted from squid ink was a well-known chemotherapeutic drug (Zhong et al., 2009). Cytotoxic tyrosinase was isolated from *S. officinalis* (Russo et al., 2003). Novel cardioactive peptides were purified from the Japanese octopus, *Octopus minor* (Iwakoshi, Hisada, & Minakata, 2000). Astaxanthin and its ester derivatives were found to be the major carotenoids in octopus and cuttlefish species (Maoka, Yokoi, & Matsuno, 1989). The Octopodidae cephalopod, *A. neglectus* was reported to contain four macrocyclic lactones **6–9** with antihypertensive potencies, among which macrocyclic lactones with furo[1,4,8]trioxacyclohexadecine-12, 19-dione functionality, **7** exhibited potent protective properties against angiotensin-II induced cardiac hypertrophy on the H9C2 cell lines (Chakraborty, Krishnan, & Joy, 2019a). Spineless cuttlefish, *S. inermis* was found to possess four chromenyl derivatives, named as methyl 7-ethyl-hexahydro-8a-methyl-2*H*-chromene-4-carboxylate **10** and methyl 1-acetoxy-hexahydro-3-methyl-3-propyl-1*H*-isochromene-4-carboxylate **11** with selective *in vitro* antioxidative/anti-inflammatory potentials (Krishnan, Chakraborty, & Joy, 2020). The same species was reported for 11-(hexahydro-8-methoxy-4-methyl-1*H*-isochromen-4-yloxy)-11-hydroxyethyl pentanoate **12** and methyl 9-(tetrahydro-3-oxo-3*H*-isochromen-5-yl)hexanoate **13** with antioxidative and antihyperglycemic potentials (Krishnan, Chakraborty, & Joy, 2019). A cephalopod mollusc, *A. marginatus* was reported with antioxidant and anti-inflammatory compounds, such as sterol derivative **14** and octahydroazulenopyrandione **15** (Chakraborty & Joy, 2018). Three antioxidative oxygenated terpenoids were reported from *U. duvauceli* with anti-inflammatory activities, and their structural attributions were elucidated as C19 furano-norditerpenoid **16**, irregular C15 sesquiterpenoid **17**, and C20 diterpenoid **18** (Chakraborty, Krishnan, & Joy, 2019).

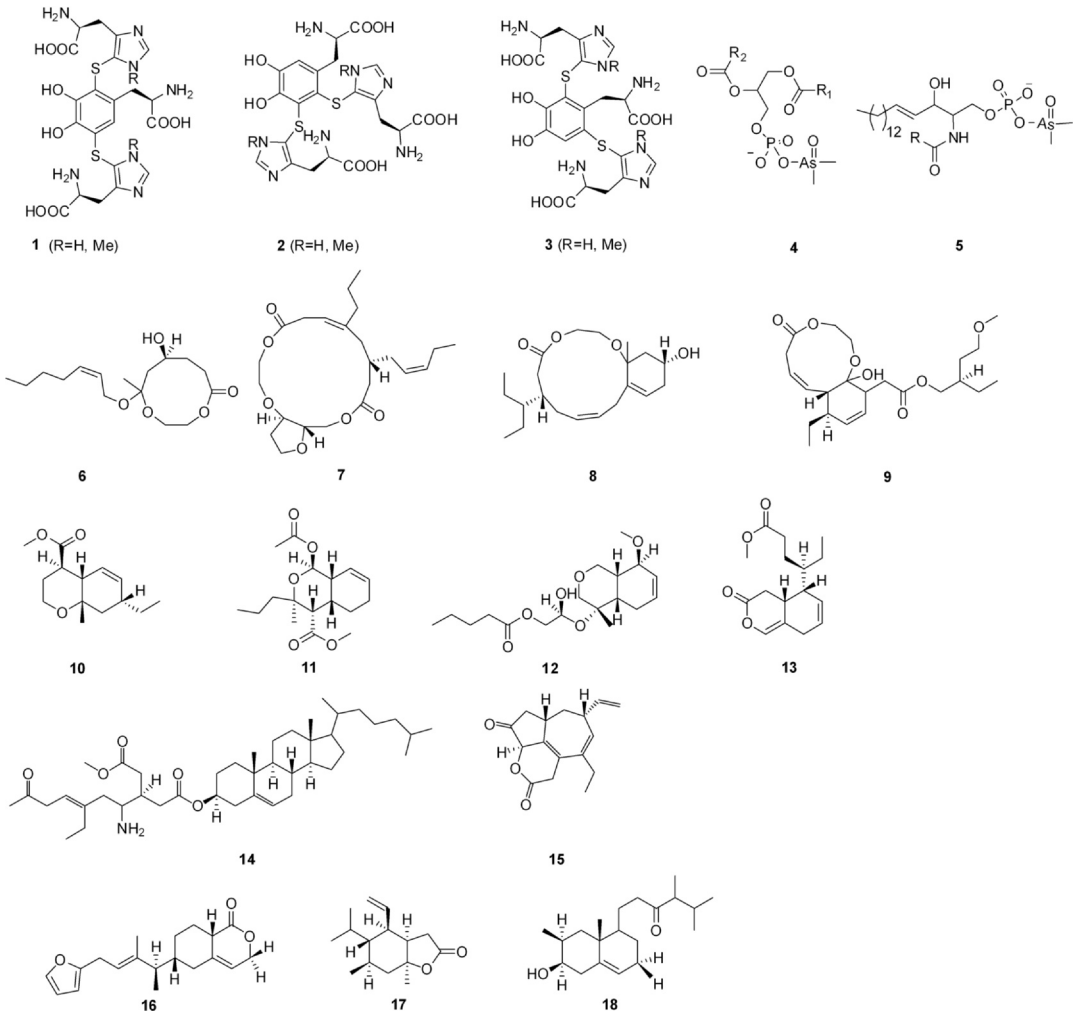


Fig. 7. Structures of compounds isolated from cephalopod molluscs. **1–3** Adenochromines, **4–5** Arsenolipids, **6–9** Macrocyclic lactones, **10–13** Chromenyl derivatives, **14** Sterol derivative, **15** Octahydroazulenopyrandione, **16–18** Oxygenated terpenoids.

6.2. Gastropod molluscs

Numerous bio-potent secondary metabolites were identified and characterized from the gastropod molluscs, and some of the important gastropod metabolites were illustrated (Figs. 8-9, S5-S10). A linear homosesterterpene, granuloside **19** was isolated from gastropod, *Charcotia granulosa* (Cutignano, Moles, Avila, & Fontana, 2015), and diterpene metabolites thuridillins **20–21** were isolated from *Thuridilla splendens* (Somerville et al., 2012). The Δ^8 unsaturated 4,4-dimethyl and 4-methyl sterols were isolated from *Cellana grata* and *C. toreuma* (Kawashima, Ohnishi, & Ogawa, 2013), and pyranone ester derivatives or analogs **22–25** were characterized from *Onchidium* sp. (Carbone et al., 2013). An anti-leishmaniasis compound, 5*α*, 8*α*-epidioxycholest-6-en-3*β*-ol was characterized from *Dolabrifera dolabrifera* (Clark et al., 2013). Mycosporine-type of amino acids **26–28** were isolated from the protective ink of *Aplysia californica* (Sea hare) (Kamio, Kicklighter, Nguyen, Germann, & Derby, 2011). The polypropionate derivatives, niuhinone A-C **29–31** were identified from the carnivorous mollusc, *Philinopsis speciosa*, and an herbivore mollusc, *Bulla occidentalis*. These suggested that the origin of these metabolites in *P. speciosa* could be due to the consumption of *Bulla* sp. (Coval, Schulte, Matsumoto, Roll, & Scheuer, 1985; Cutignano, Calado, Gaspar, Cimino, & Fontana, 2011). A guanidine-bound terpene derivative **32** was identified from *Doto pinnatida* (Putz, Kehraus, Diaz-Agras, Wagele, & Konig, 2011), whereas an asteriscane sesquiterpenoid **33** was characterized from *Phyllodesmium magnum* (Mao, Gavagnin, Mollo, & Guo, 2011). Rare pyran-enclosed cladiellane diterpene derivatives, tritoniopsin A-D **34–37** were isolated from *Tritoniopsis elegans* and its feed *Cladiella krempfi* (coral) (Ciavatta et al., 2011). Novel diterpenoids **38–39** and chromoculatimine A-B **40–41** were identified, and tissue localization studies revealed that these diterpenes were obtained from their mantle and internal organs (Suciati, Lambert, & Garson, 2011). An isopentyl-containing alkaloid, tambjamine K **42** was identified from *Tambja ceutae* (Carbone et al., 2010). The clerodane diterpenes palmadorin A-C **43–45** were isolated from a nudibranch, *Austrodoris kerguelenensis* (Diyabalanage, Iken, McClintock, Amsler, & Baker, 2010) and sesterterpenoid, ansellone A **46** was isolated from *Cadlinalutero marginata* (Daoust et al., 2010). Extraction of digestive and hermaphroditic glands of *Aplysia fasciata* (sea hare) yielded sesquiterpenoids **47–49**, acetogenin **50**, and diterpenoid **51** (Ioannou, Nappo, Avila, Vagias, & Roussis, 2009).

The *α*-pyrone polyketides, aplysiopsene A-D **52–55** were isolated from herbivorous *Aplysiopsis formosa* (slug) (Ciavatta et al., 2009). Chemical investigation of *Chromodoris willani* reported for its deoxy analogs of manoalide **56** and secomanoalide **57** with antimicrobial activity (Uddin et al., 2009). An antifungal compound kabiramide B was reported from the Pacific nudibranch *Hexabranchuss anguineus* (Matsunaga et al., 1989). The prosobranch mollusc, *Onchidiopsis variegate* was reported for the presence of ketosteroid derivative **58** (Santalova, Denisenko, Chernyshev, Gavagnin, & Sanamyan, 2007), and sacoglossan mollusc, *Elysia grandifolia* was reported to harbor two new members of cyclic depsipeptides **59–60** in the kahalalide family

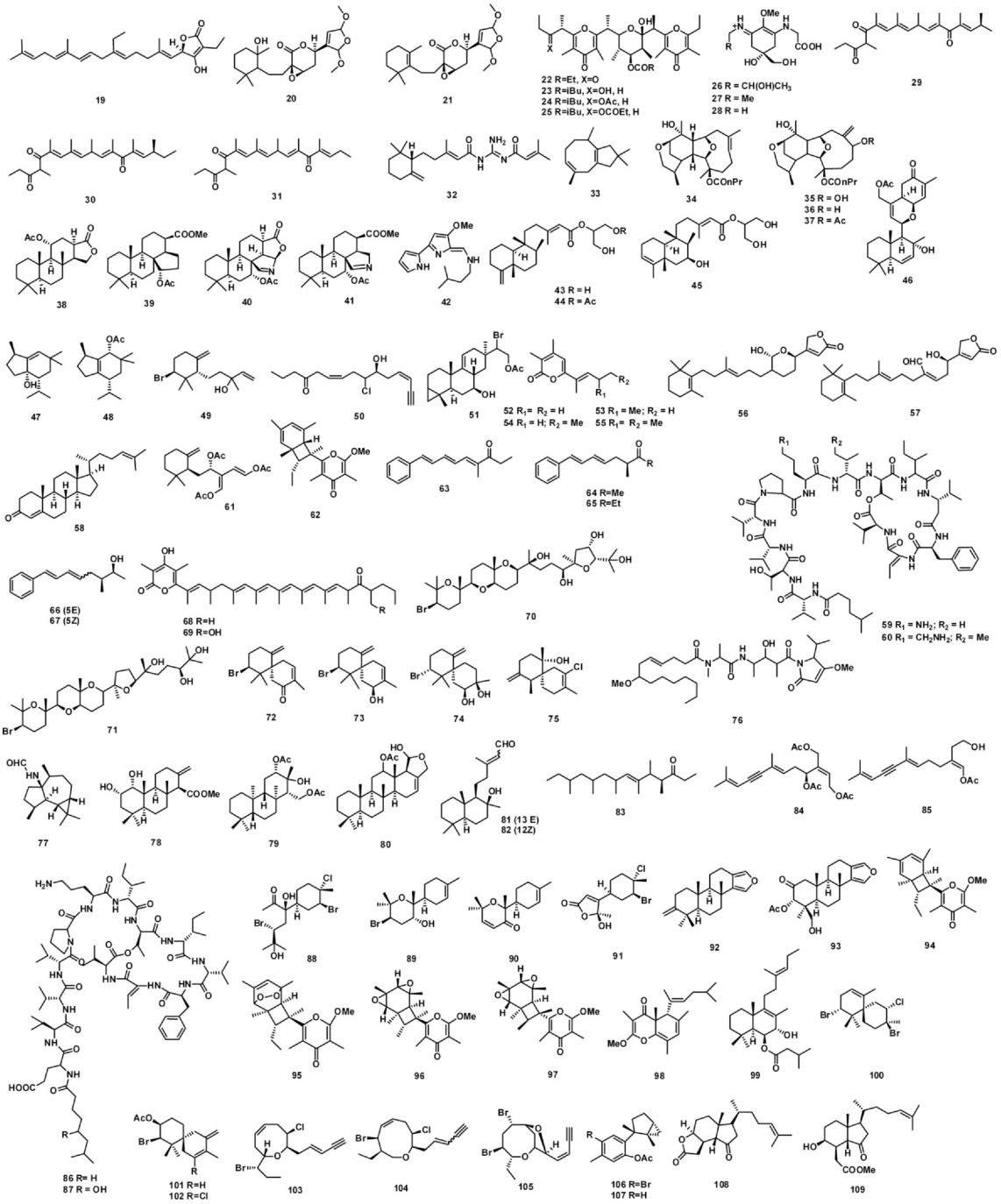


Fig. 8. Structures of compounds isolated from gastropod molluscs. **19** Homosesterterpene, granuloside, **20–21** Thuridillins, **22–25** Pyranone ester derivatives, **26–28** Mycosporine-type amino acids, **29–31** Polypropionate derivatives, niuhinone A-C, **32** Guanidine-bound terpene derivative, **33** Asteriscane sesquiterpenoid, **34–37** Tritoniopsin A-D, **38–39** Diterpenoids, **40–41** Chromoculatimine A-B, **42** Tambjamine K, **43–45** palmadorin A-C, **46** Ansellone A, **47–49** Sesquiterpenoids, **50** Acetogenin, **51** Diterpenoid, **52–55** Aplysiopsene A-D, **56** Manoalide, **57** Secomanoalide, **58** Ketosteroid derivatives, **59–60** Cyclic depsipeptides, **61** Crispatenine, **62** Pyrone compound, **63–67** Lignarenones, **68–69** Fusaripyrones, **70–71** Aplysiols, **72–75** Chamigrane sesquiterpenoids, **76** Malyngamide, **77** Sesquiterpenoid, **78** Diterpenoid, **79** Isocopalane diester, **80** Scalarane, **81–82** Labdane, **83** Siphonarienolone, **84–85** Caulerpenyne metabolites, **86–87** Kahalalide R-S, **88–91** Bisabolene typed sesquiterpenes, **92–93** Miscellaneous, **94–95** Pyrone and its possible peroxy analog, **96–97** Elysiapyrone metabolites A-B, **98** Tridachiahydropyrone, **99** *Trans*-decalin, **100–102** Sesquiterpene derivatives, **103–104** C15-halogenated derivatives, **105** (3*Z*)-bromofucin, **106** Laurinterol, **107** Debromolaurinterol, **108–109** Degraded sterols.

(Tilvi & Naik, 2007). Absolute conformation of crispatenine (sesquiterpenoid), **61** formerly identified from *Tridachia crispata* (Gavagnin et al., 1997), was recognized by its enantioselective synthesis (Bourdron et al., 2007). A new pyrone compound **62** was reported from *Placobranchus ocellatus* (Manzo et al., 2005a), and aromatic benzene-enclosed compounds, named as lignarenones, were reported from *Scaphander lignarius* **63–67** (Sala et al., 2007). The polypropionate analogs, fusaripyrones A and B **68–69** were reported from Mediterranean *Haminoea fusari* (Cutignano et al., 2007). Polyether triterpenes, named as aplysiols A and B **70–71** were identified from *Aplysia dactylomela* (sea hare) collected from the South China Sea (Manzo et al., 2007a), and the chemical investigation of this same species from

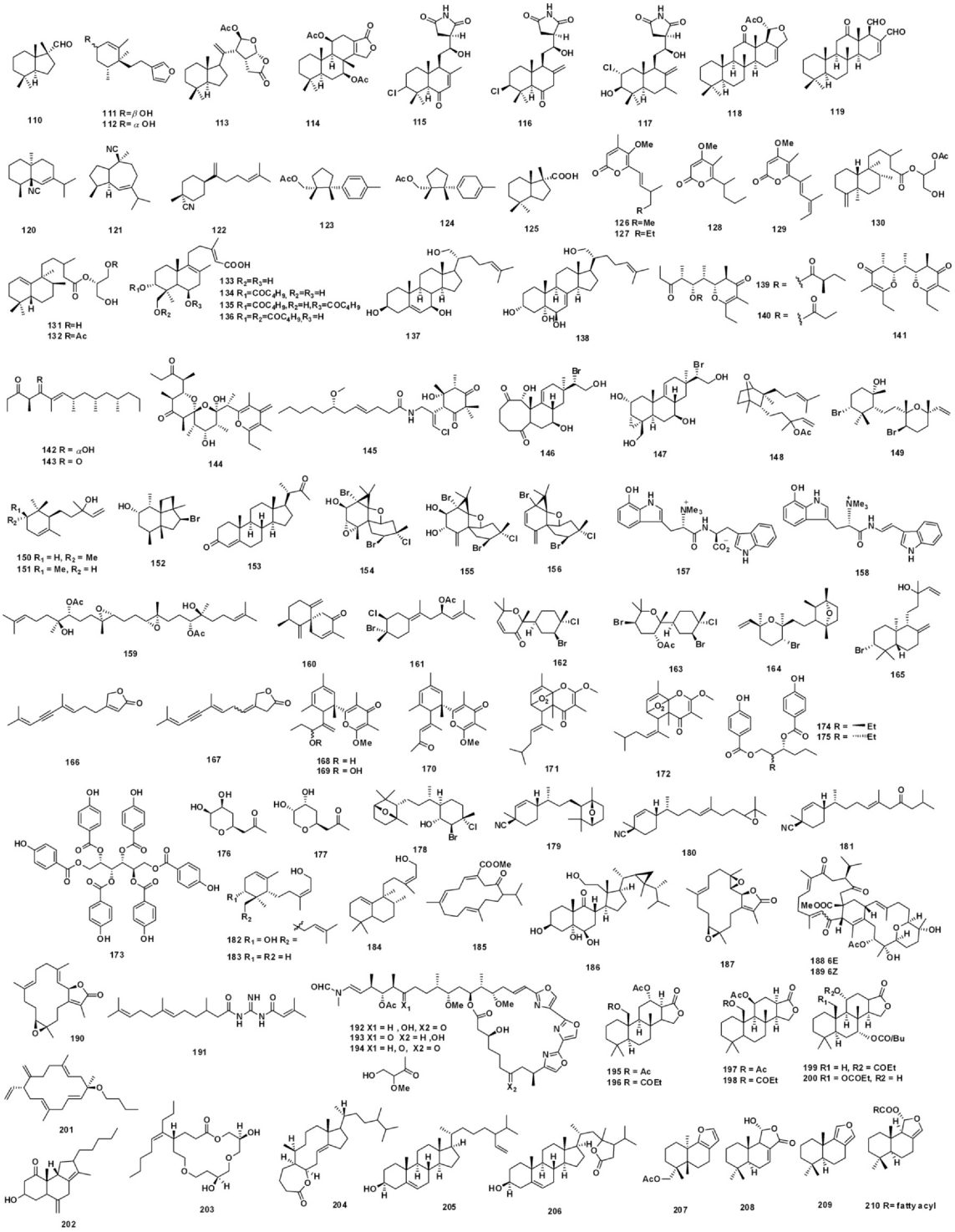


Fig. 9. Structures of compounds isolated from gastropod molluscs. **110** (+)-Austrodoral, **111–112** Pelseneeriols, **113** Norrisolide, **114** Dorisenone C, **115–116** Haterumaimides, **117** 3β-Hydroxychlorolissoclimide, **118–119** Scalarane metabolites, **120–122** Sesquiterpenes, **123** (−)-Tochuinyl acetate, **124** (−)-Dihydrotochuinyl acetate, **125** Austrodoric acid, **126–129** Placidenes C-F, **130–132** Acylglycerols, **133–136** Labdane diterpenes, **137–138** Polyhydroxylated steroids, **139–140** Membrenones A-C, **142** Siphonarienolone, **143** Siphonarienedione, **144** Siphonarin B, **145** Malyngamide-S derivative, **146–149** Diterpene metabolites, **150–152** Sesquiterpenes, **153** Progesterone analog, **154** Johnstonol, **155** Pacifenediol, **156** Pacifidiene, **157–158** Tryptophan-based dipeptides, **159** Auriculol, **160** Non-halogenated sesquiterpene, **161** Puertitol-B acetate, **162** Caespitenone, **163** 8-Acetyl-caespitol, **164** Dactylopyranoid, **165** Isopinnatol B, **166–167** Ascobullins A-B, **168–170** Tridachiapyrones G-J, **171–172** Tridachiahydro pyrones B-C, **173** Scutinin A, **174–175** Scutinin B epimers, **176–177** Tetrahydropyran monodontins A and B, **178** Bromo-chloro-diterpenoid dolabellol A, **179–181** Pustulosaisonitriles 1–3, **182** Spurillin A, **183** Farnesol derivative, **184** Diterpene spurillin B, **185** Methylsarcoate analog, **186** 2R Secogorgosterol, **187** Bisepoxide, **188–189** Isobisglaucumlides B-C, **190** Isosarcophine, **191** Diacylguanidine actinofide, **192–194** Ulapualides C-E, **195–200** Spongian-16-one analogs, **201** Cembrane-type diterpenoid, **202** Sesquiterpenoid Ramosane, **203** Polyether macrocyclic lactone, **204** Lactonic steroid, **205–206** Unusual Δ^5 sterols, **207** 15-Acetoxy-ent-pallescensin-A, **208** Dendocarbin-A, **209** Euryfuran, **210** Drimane ester.

Madagascar afforded halogenated chamigrane sesquiterpenoids **72–75** (Shubina et al., 2007). Another sea hare, *Bursatella leachii* was reported to produce 7*R*-configured malyngamide **76** (Suntornchashwej, Suwanborirux, Koga, & Isobe, 2007). A sesquiterpenoid **77** and a diterpenoid **78** were isolated from *H. sanguineus* (Spanish dancer mollusc) (Zhang et al., 2007). The isocopalane diester **79** was isolated from a previously unrevealed gastropod of Marion Island (van Wyk, Froneman, Bernard, & Davies-Coleman, 2007). A 12-keto scalarane type of compound, **80** was reported from *Glossodoris averni* (Queensland, Australia), and *G. pallida* (Hainan, China) (Manzo et al., 2007b). The labdane class of diterpenoids **81–82** were reported from *Plevrobranchaea meckelii* (Ciavatta, Villam, Trivellone, & Cimino, 1995). The pulmonate, *Siphonaria lessoni* was the major source of a nor-homolog of well-known metabolite, siphonarienolone **83** (Rovirosa & San-Martin, 2006). A cytotoxic alkaloid lamellarin N was reported from *Lamellaria* sp., and further structure–activity analyses on lamellarin D were carried out (Pla et al., 2006). The sacoglossan mollusc, *Elysia* cf. *expansa* collected from Mandapam, India afforded two caulerpenyne-type metabolites, dihydrocaulerpenyne **84** and expansinol **85** (Ciavatta et al., 2006).

The cyclic depsipeptides, kahalalide R-S, **86–87** were reported from *E. grandifolia* (Ashour et al., 2006). Bisabolene-type sesquiterpenes **88–91** were identified from the crude extracts of *A. dactylomela* (Brito, Dias, Diaz-Marrero, Darias, & Cueto, 2006). An antitumor compound, aplyronine A was isolated from *A. kurodai* (Yamada, Ojika, Ishigaki, & Yoshida, 1993). Chemical investigation of Australian mollusc, *Glossodoris atromarginata* was found to possess the compounds, **92** and **93**, for the first time (Andersen, Desjardine, & Woods, 2006). The pyrone **94** and its possible peroxy analog **95** from *Placobranchus ocellatus* were reported previously (Manzo et al., 2005a). Cueto, D'Croz, Mate, San-Martin, and Darias (2005) reported the presence of elysiapyrone metabolites A-B **96–97** from *Elysia diomedea*. The tridachiahydropyrone metabolite, **98** was isolated from *T. crispata* and a *trans*-decalin compound, **99** was isolated from *T. reticulatus* (Gavagnin, Mollo, Cimino, & Ortea, 1996; Manker & Faulkner, 1987). Sesquiterpene derivatives **100–102** were isolated from *A. dactylomela* (Dias et al., 2005) with *in vitro* antitumor activity. The C15-halogenated derivatives **103–104** were identified from *A. dactylomela* (Manzo et al., 2005b). The metabolite (3*Z*)-bromofucin **105** was isolated from *A. parvula* extracts (McPhail & Davies-Coleman, 2005), whereas the bioactive laurinterol **106** and debromolaurinterol **107** were reported from *A. kurodai* (Tsukamoto, Yamashita, & Ohta, 2005). *B. leachii* was the predominant source of cytotoxic metabolites, such as hectochlorin and deacetyl derivatives (Suntornchashwej, Chaichit, Isobe, & Suwanborirux, 2005). The degraded sterols, such as aplykurodinone 1–2 (**108** and **109**) were purified from the skin extract of mollusc, *Syphonota geographica* (Gavagnin et al., 2005). Derivatives of dolastatin 11 from *D. auricularia* (Pettit et al., 1989) and nor-sesquiterpenoid, (+)-austrodoral **110** from *A. kerguelenensis* (Antarctic mollusc) were previously reported (Gavagnin, Carbone, Mollo, & Cimino, 2003). Furanosesquiterpene alcohol derivatives, pelseneeriols-1 **111** and 2 **112** were reported from *Doriopsilla pelseneeri* (Gaspar et al., 2005). Dodecadienonyl-benzoquinone and hydroquinone derivatives were purified from *Leminda millecra* (African gastropod) (McPhail, Davies-Coleman, & Starmer, 2001). Norrisolide **113** was isolated from *Chromodoris norrisi* (Hochlowski, Faulkner, Matsumoto, & Clardy, 1983) and dorisenone C **114** was identified from *C. obsolete* (Miyamoto et al., 1996). The cytotoxic components, haterumaimides L **115** and M **116** along with 3β-hydroxychlorolissoclimide **117** were obtained from *Pleurobranchus albiguttatus* and *P. forskalii* (Fu, Palomar, Hong, Schmitz, & Valeriote, 2004).

Isolation of scalarane-framework metabolites **118** and **119** from *G. rufomarginata* was described in a previous report of literature (Gavagnin, Mollo, Docimo, Guo, & Cimino, 2004). Sesquiterpenes **120–122** were fractionated from *Phyllidiella pustulosa* found at South China (Manzo et al., 2004). The sesquiterpenes (−)-tochuinyl acetate **123** and (−)-dihydrotochuinyl acetate **124** were identified from *Tochuina tetraquetra* (Williams & Andersen, 1987). Pyrone polypropionate, cyercene was reported by Vardaro, Di Marzo, Crispino, and Cimino (1991) from the Mediterranean *Cyerce cristallina*. Austrodoric acid **125** from Antarctic *A. kerguelenensis* was previously reported by Gavagnin, Carbone, Mollo, and Cimino (2003). Asymmetrical polypropionate derivatives named as placidenes C-F **126–129** were characterized by Cutignano, Fontana, Renzulli, and Cimino (2003) from *Placida dendritica*. Chemical investigation of diterpenoid acylglycerol fraction from the Antarctic gastropod, *A. kerguelenensis* yielded acylglycerols **130–132** (Gavagnin, Carbone, Mollo, & Cimino, 2003). Labdane diterpenes **133–136** were identified from *T. peruvianus* (pulmonate) along with cytotoxic polyhydroxylated steroids **137–138** (Diaz-Marrero et al., 2003a, 2003). Three polypropionate enclosed compounds, named as membrenones A-C **139–141** were extracted from *Pleurobranchus membranaceus* by Ciavatta, Trivellone, Villani, & Cimino, 1993. Chemical investigation of *Siphonaria grisea* reported the presence of polypropionates, which were named as siphonarienolone **142** and siphonarienedione **143** (Calter & Liao, 2002), and their stereochemistries were also established (Norte, Cataldo, Gonzalez, Rodriguez, & Ruiz-Perez, 1990). Siphonarin B **144** was reported from *Siphonaria zelandica* and *S. atra* (Hochlowski et al., 1984). A novel malyngamide S derivative **145** was reported from the mollusc *B. leachii*, and the compound was found to exhibit potential anti-inflammatory activities (Appleton, Sewell, Berridge, & Copp, 2002). Wide range of diterpene metabolites **146–149** and new sesquiterpenes **150–152** were reported by Findlay and Li (2002) from the Sardinian Sea hare *Aplysia punctata*. The progesterone analog **153** was isolated by Gavagnin, Ungur, Mollo, Templado, and Cimino (2002), from the nudibranch *Aldisas maragdina* (Spain). Extensive NMR assignments of the *A. dactylomela* metabolites, such as johnstonol **154**, pacifenediol **155** and pacifidiene **156** (Kaiser, Pitombo, & Pinto, 2001), along with tryptophan-based dipeptides **157** and **158** (Appleton, Babcock, & Copp, 2001), were previously reported. Another sea hare, *Dolabella auricularia* was found to contain a novel cytotoxic squalene metabolite, named as auriculol **159** (Kigoshi, Hayashi, & Uemura, 2001). A non-halogenated sesquiterpene **160** was found from *Aplysia* sp., which was possibly a rearranged product of a known chamigrane (Fedorov, Shubina, Kalinovsky, Lyakhova, & Stonik, 2000). New sesquiterpenes, puertitol-B acetate **161**, caespitenone **162** and 8-acetyl-caespitol **163**, along with diterpenoids, such as dactylopyranoid **164** and isopinnatol B **165** with prospective bioactivity profiles were characterized from *A. dactylomela* (Wessels, Konig, & Wright, 2000). The sesquiterpene metabolites, ascobullins A **166** and B **167** were reported from *Asco bullaulla* (Gavagnin, Mollo, Montanaro, Ortea, & Cimino, 2000). Polypropionate pyrones, such as tridachiapyrones G-J **168–170** and tridachiahydropyrones B-C **171–172** were reported from the mollusc, *P. ocellatus* (Fu, Hong, & Schmitz, 2000).

The unreported odd-chain fatty acids were identified from the ovaries of *Cellana toreuma*, and their structures were confirmed by synthesis (Shimada, Sugawara, Korenaga, & Kawashima, 2017). The Australian samples of *Scutus antipodes* afforded scutinin A **173** and scutinin B as epimers **174–175** with antibacterial and antifungal properties (Chand & Karuso, 2017). Tetrahydropyrans, which were named as monodontins A and B **176–177** exhibiting weak cytotoxicities, were reported from the Vietnamese snail *Monodonta labio* (Huong et al., 2017). A bromo-chloro-diterpenoid dolabellol A **178** was identified from *D. auricularia*, and its structure and absolute configuration were confirmed through X-ray diffraction (MacHida, Matsumoto, Fusetani, & Nakao, 2017). The isonitriles, named as pustulosaisonitriles 1–3 **179–181** were isolated from *Phyllidiella pustulosa* (White et al., 2017). *Spurilla neapolitana* from Bay of Naples afforded cyclohexenyl terpenoid, named as spurillin A **182**, whereas *Spurilla* sp. from Patagonian collection was reported with a farnesol derivative **183** and diterpene spurillin B **184** (Ciavatta et al., 2017). The methylsarcoate analog **185**, 2R secogorgosterol **186**, bisepoxide **187**, isobisglaucumlides B-C **188–189** and isosarcophine **190** were isolated from *Phyllodesmium longicirrum* (Bogdanov et al., 2017). A

diacylguanidine actinofide **191** with moderately antiproliferative activity was reported from *Actinocyclus papillatus* (Carbone et al., 2017), and three ulapualides, C-E **192–194** were isolated from the Hawaiian *H. sanguineus* (Parrish, Yoshida, Yang, & Williams, 2017). *Goniobranchus collingwoodi* was reported to yield spongian-16-one analogs **195–200** (Forster et al., 2017), and 6-bromoisatin, and its analogs with anti-inflammatory activities were reported from *Dicathais orbita* (Ahmad et al., 2017). Chemical investigation of the organic extract of muricid gastropod mollusc, *C. ramosus* reported the presence of cembrane-type diterpenoid **201** with anti-inflammatory and antioxidative properties (Chakraborty, Salas, & Joy, 2020). An antioxidative drimane-type sesquiterpenoid, ramosane **202**, which attenuated the carbolytic and 5-lipoxygenase enzymes, was isolated from *C. ramosus* (Chakraborty & Salas, 2019). A 16-membered polyether macrocyclic lactone **203** with previously undescribed framework with antilipoxygenase and antioxidative potentials were reported from the organic extract of Babylonidae gastropod, *B. spirata* (Salas & Chakraborty, 2018a). A lactonic steroid with an unprecedented 1, 10:8, 9-disecoergostane framework, named as 1, 10:8, 9-disecoergosta-8-en-*α*-homo-6a-oxa-1-one **204** was identified from a buccinid mollusc, *B. spirata* with anti-inflammatory and carbolytic enzyme inhibition activities (Chakraborty, Joy, & Salas, 2019), whereas two unusual Δ^5 sterols **205–206** were reported from *C. ramosus* with anti-inflammatory potential (Salas & Chakraborty, 2018b). The porostome nudibranch *D. pelseneeri* was reported with 15-acetoxy-ent-pallescensin-A **207**, and dendocarbin-A **208** from its mantle, whereas euryfuran **209** and drimane ester mixture **210** were identified from its internal glands (Gaspar et al., 2005).

6.3. Bivalve molluscs

Bivalves occupied a highest share in the hierarchy of total edible molluscs, although they were not extensively recognized for their pharmaceutical and biomedical properties (Mohite, Mohite, & Singh, 2009). Earlier reports demonstrated that the bivalves possessed numerous compounds (Figs. 10-11, S11-15) with wide-range of bioactive properties (Benkendorff, 2010; Chakraborty et al., 2014; Nagash, Nazeer, & Kumar, 2010). A novel sequence of *n*-4 PUFAs **211–216** were identified from *Calyptogena phaseoliformis* (deep-sea clam) collected from the Japan Trench (Saito, 2007). The hard clam, *M. lusoria* (Taiwan), which was reported with two epidioxysterols **217–218** with anticancer properties, was the primary resource of the Chinese antidote for hepatitis and liver illness (Pan, Huang, Chang, Ho, & Pan, 2007). New thio-arsenosugars, **219** and **220** were identified from the extracts of brackishwater clam, *Venus verrucosa* (Nischwitz, Kanaki, & Pergantis, 2006). Isolation and characterization of *N*-methyl-D-glutamic acid **221** from the Japanese Ark clam, *Scapharca broughtonii* was the first report of this kind of amino acid derivative as natural compound (Tarui et al., 2003). The clam, *Callista chione* was reported to contain 1,1′-dimethyl-[2, 2′]-bipyridyldiium salt **222**, which was acknowledged for the first time from a natural resource (Vagias, Tsitsimpikou, Rapti, & Roussis, 2000). The terpenoid constituent from *Tridacna maxima* (giant clam) was found to be germacrene-C **223** (Bowden, Coll, & Mitchell, 1980). An arsenic-enclosed sugar sulphate **224** was isolated from *T. maxima*, and was characterized by X-ray crystallography (Edmonds, Francesconi, Healy, & White, 1982). A new antioxidative pigment, chlorophyllone A **225** was isolated from the short-necked clam, *R. philippinarum* (Sakata et al., 1990). An arsenic containing nucleoside, 5′-deoxy-5′-dimethylarsinyl-adenosine **226** was isolated from *T. maxima* (Francesconi, Stick, & Edmonds, 1991). The antioxidant, chlorophyllonic acid A methyl ester **227** was identified from *R. philippinarum* by single crystal X-ray diffraction (Yamamoto et al., 1992). Peridininol-5, 8-furanoxide **228**, 7,8-didehydro-β-cryptoxanthin **229**, peridinin **230**, pyrrhoxanthin 5,8-furanoxide **231**, pyrrhoxanthinol-5, 8-furanoxide **232** and lutein **233** were the main carotenoids found in molluscs (Maoka, Fujiwara, Hashimoto, & Akimoto, 2005a, 2005b). The 6-epiheteroxanthin **234**, corbiculaxanthin-3′-acetate **235** and corbiculaxanthin **236** isolated from these species were not reported previously from other shellfishes (Maoka, Fujiwara, Hashimoto, & Akimoto, 2005). A series of fucoxanthin **237–242** and fucoxanthinol **243–244** fatty acid esters were identified from *M. chinensis* (Chinese surf clam) (Maoka, Fujiwara, Hashimoto, & Akimoto, 2007), *R. philippinarum* and *M. petechialis* (Maoka, Akimoto, Murakoshi, Sugiyama, & Nishino, 2010). Amarouciaxanthin A **245** and its ester derivatives were identified from *Paphia amabills* and *P. amabillis* along with C37-skeletal carotenoids **246–249** (Maoka, Akimoto, Yim, Hosokawa, & Miyashita, 2008). The bivalve mollusc, *Codakia orbicularis* was found to be the source of spiroindolothiazine orbicularisine (Goudou, Petit, Moriou, Gros, & Al-Mourabit, 2017).

The sterol derivatives namely, 23-*gem*-dimethylcholestaenol **250** and methyldihomocholest-5, 22-dienol **251** with antioxidative and anti-inflammatory properties were reported from the venerid bivalve clam, *P. malabarica* collected from the south-west coast of Arabian Sea (Joy, Chakraborty, & Raola, 2017). Corbiculid clam, *V. cyprinoides* was reported with one *abeo*-pregnane-type sterol derivative, named as 19 (10 → 5) *abeo*-20-methyl-pregnenyl-3-hexenoate **252** along with two cholestenols, 24^1, 24^2-dihomocholesta-5, 22, 24^1-trienol **253** and 24^1-homocholesta-5, 22-dien-3, 24^1-diol **254** (Joy & Chakraborty, 2018a). Chemical investigations of organic extract of *P. malabarica* was reported the presence of two 2*H*-pyranoids, in which, one was found to be C18 sesquiterpenoid with prenylated irregular farnesene framework **255**, and another was a C21 prenylated bisabolene-type meroterpenoid, **256** (Joy & Chakraborty, 2017). The same species was reported for the presence of an isopimarane derivative, which was found to be 18 (4 → 14), 19 (4 → 8)-bis-*abeo* C19 norditerpenoid **257** (Joy & Chakraborty, 2017), and two chromenyls bearing 3*H*-isochromenone **258** and furanyl-2*H*-chromenyl **259** moieties (Joy & Chakraborty, 2017d). Antioxidative and anti-inflammatory aryl polyketides **260–262** were identified from *P. malabarica,* and their proposed biosynthetic pathways assisted by polyketide synthase were used to validate their structural attributions (Joy & Chakraborty, 2017e). These compounds could be the effective substitutes for the commercial synthetic antioxidative food additives for the improvement of shelf-life of foods, and prevention of oxidative stress-induced inflammatory ailments (Joy & Chakraborty, 2017e). The pyranoids **263–264** and isochromenyl **265–266** class of compounds (Joy & Chakraborty, 2018b), along with oxygenated heterocyclics were classified as *O*-spirocyclic ether derivatives **267–268**, and an irregular meroterpenoid derivative **269** were reported from *V. cyprinoides* with antioxidative and anti-inflammatory functionalities (Joy & Chakraborty, 2018c).

Several carotenoids **270–272** were isolated from *M. galloprovincialis* collected from the Black Sea of Ukraine (Maoka, Etoh, Borodina, & Soldatov, 2011). The bathymodiolamides A **273** and B **274** with antitumor potentials were isolated from a deep-sea mussel, *Bathymodiolus thermophiles* (Andrianasolo et al., 2011). An antimicrobial peptide, mytilin-A was purified from the bivalve *M. edulis*, and the peptide analog exhibited potential bioctivity towards marine *Vibrio*, yeasts, and fungi (Charlet et al., 1996). A homologous series of *n*-3 PUFAs along with 7, 11, 14, 17-eicosatetraenoic acid **275** were identified as anti-inflammatory components in the New Zealand green-lipped mussel *P. canaliculus* (Treschow et al., 2007). The compound, 20-methyl spirolide G **276** was identified from *M. edulis* (Aasen et al., 2005). Chromatographic fractionation of *M. galloprovincialis* extracts were found to yield a chlorosulfolipid **277** (Ciminiello et al., 2004). Undescribed azaspiracid analogs **278–282** were characterized by tandem mass spectrometric methods from *M. edulis* (Ireland) (James, Sierra, Lehane, Magdalena, & Furey, 2003). Structure of polychlorinated sulfolipid **283** was reported from *M. galloprovincialis* (Ciminiello et al., 2002) and the spiro-acetals, attenols A **284** and B **285** were isolated from *Pinna attenuate* (Takada et al., 1999). New bioactive alkaloids, oxazinins 1–3 **286–288** were identified from *M. galloprovincialis* (Ciminiello et al., 2001). The macrolides, spirolides B-C **289–290** were isolated from *M. edilis* (Hu et al., 1995), and the mycosporine derivatives, such as mytilin

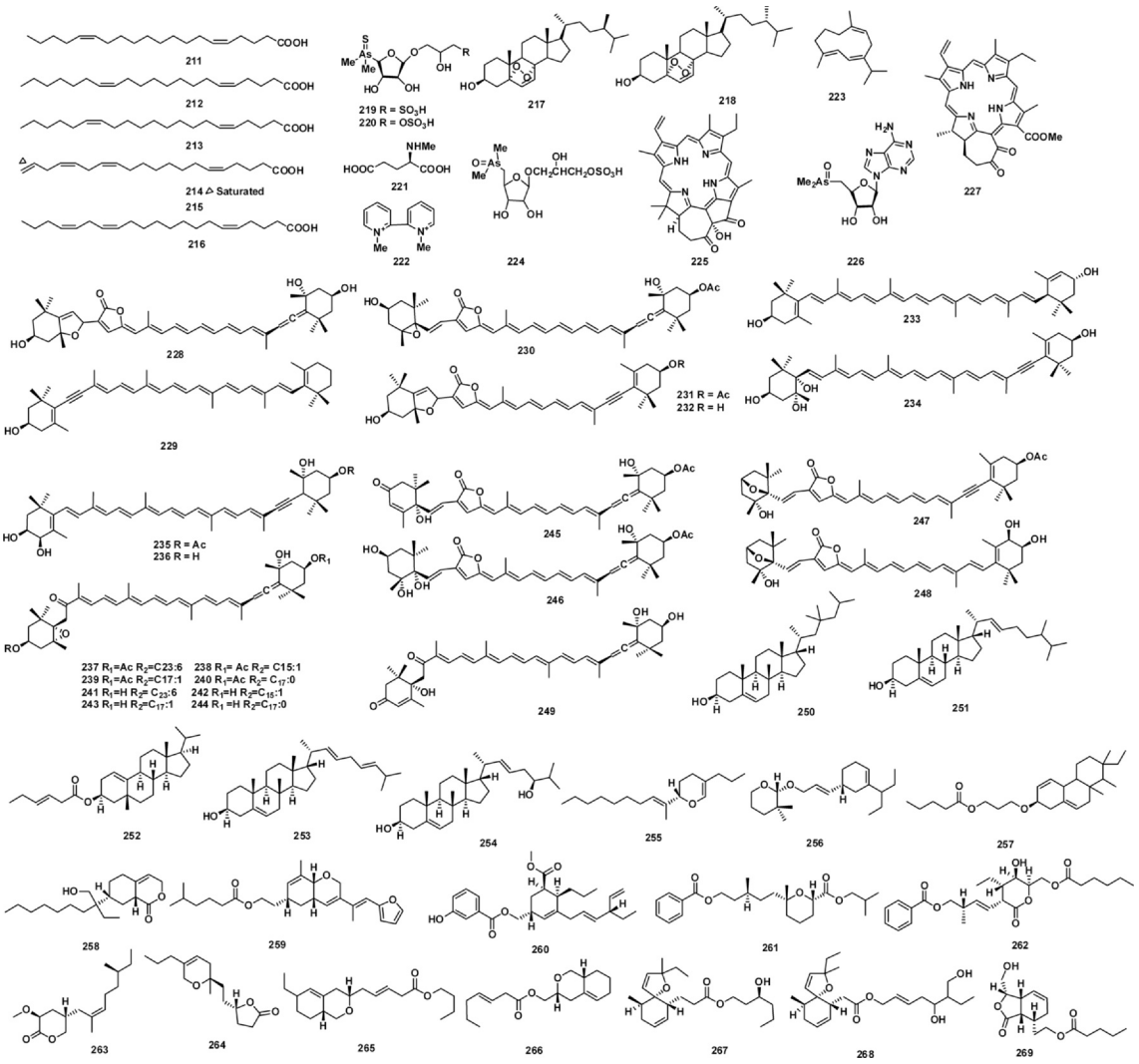


Fig. 10. Structures of compounds isolated from bivalve clams. **211–216***n* -4 PUFAs, **217–218** Epidioxysterols, **219–220** Thioarsenosugars, **221** *N*-methyl-D-glutamic acid, **222** 1, 1′-Dimethyl-[2, 2′]-bipyridyldiium salt, **223** Germacrene-C, **224** Arsenic-enclosed sugar sulfate, **225** Chlorophyllone A, **226** 5′-Deoxy-5′-dimethylarsinyl-adenosine, **227** Chlorophyllonic acid A methyl ester, **228** Peridininol-5, 8-furanoxide, **229** 7, 8-Didehydro-*β*-cryptoxanthin, **230** Peridinin, **231** Pyrrhoxanthin 5, 8-furanoxide, **232** Pyrrhoxanthinol-5, 8-furanoxide, **233** Lutein, **234** 6-Epiheteroxanthin, **235** Corbiculaxanthin-3′-acetate, **236** Corbiculaxanthin, **237–242** Fucoxanthin, **243–244** Fucoxanthinol, **245** Amarouciaxanthin A, **246–249** Carotenoids, **250** 23-*Gem*-dimethylcholestaenol, **251** Methyl-dihomocholest-5, 22-dienol, **252** 19 (10 → 5) *Abeo*-20-methyl-pregnenyl-3-hexenoate, **253** 24[1], 24[2]-Dihomocholesta-5, 22, 24[1]-trienol, **254** 24[1]-Homocholesta-5, 22-dien-3, 24[1]-diol, **255–256** 2*H*-Pyranoids, **257** Isopimarane derivative, **258–259** Chromenyls, **260–262** Aryl polyketides, **263–264** Pyranoids, **265–266** Isochromenyls, **267–268***O* -spirocyclic ether derivatives, **269** Irregular meroterpenoid derivative.

A **291** and B **292** were acquired from *M. galloprovincialis* (Chioccara, Misuraca, Novellino, & Prota, 1979). The apocarotenoid, apoalloxanthinal **293** was isolated from *M. coruscus* (Maoka, 1997), and cytosolic phospholipase A2 inhibitors, pinnaic acid **294** and tauropinnaic acid **295** were isolated from *P. muricata* (Chou et al., 1996). Spirolides E **296** and F **297** metabolites from *M. edulis* could help defining the characteristic structural features of this class of compounds (Hu, Curtis, Walter, & Wright, 1996). Two dodecahydro-phenanthrenone derivatives **298–299**, benzo[*h*]naphtho[1,2-*c*]chromene derivatives **300–301**, and two sterol analogs **302–303** were isolated from the Asian green mussel, *P. viridis*. Among these, the compounds with chromene-16-carbaldehyde and chromen-12-one **300–301** functionalities displayed potential anti-inflammatory activities (Chakraborty, Joy, & Chakkalakal, 2018).

Ostrerine A **304** was reported from *O. rivularis*, and was used as foodstuff and conventional Chinese medication (Ouyang, 2006). The carotenoids **305–307** were reported from *C. gigas* (Japan) (Maoka, Fujiwara, Hashimoto, & Akimoto, 2005), whereas an antimicrobial peptide, defensin (molecular weight of 4265 Da) was isolated from the oyster, *C. virginica* (Seo, Crawford, Stone, & Noga, 2005). The carotenoids **308–312** were reported from *C. gigas* (Maoka, Hashimoto, Akimoto, & Fujiwara, 2001). Metabolites of fucoxanthin, crasssostreaxanthin A **313** and crassostreaxanthin B **314** (Fujiwara, Maoka, Ookubo, & Matsuno, 1992), along with C37-skeletal carotenoids were identified from the mollusc *C. gigas* (Maoka, Fujiwara, Hashimoto, & Akimoto, 2005). A polyphenolic compound, 3, 5-dihydroxy-4-methoxybenzyl alcohol **315** was identified from the Pacific edible oyster (*C. gigas*), and its potential antioxidant activity was determined (Watanabe et al., 2012). Chemical investigations of the solvent extract of *C. madrasensis* reported two phenylacetyloxy-trimethylpicene-23-carboxylate **316–317** derivatives with potential anti-inflammatory and antioxidant activities (Chakraborty & Joy, 2018). The macrolides, spirolides B **318** and D **319** were reported from a scallop, *Placopecten magellanicus* (Hu et al., 1995), whereas spirolides E and F were isolated from the scallop *P. magellanicus* (Hu, Curtis, Walter, & Wright, 1996). Metabolites of alloxanthin and diatoxanthin, such as pectenol **320**, pectenolone **321**,

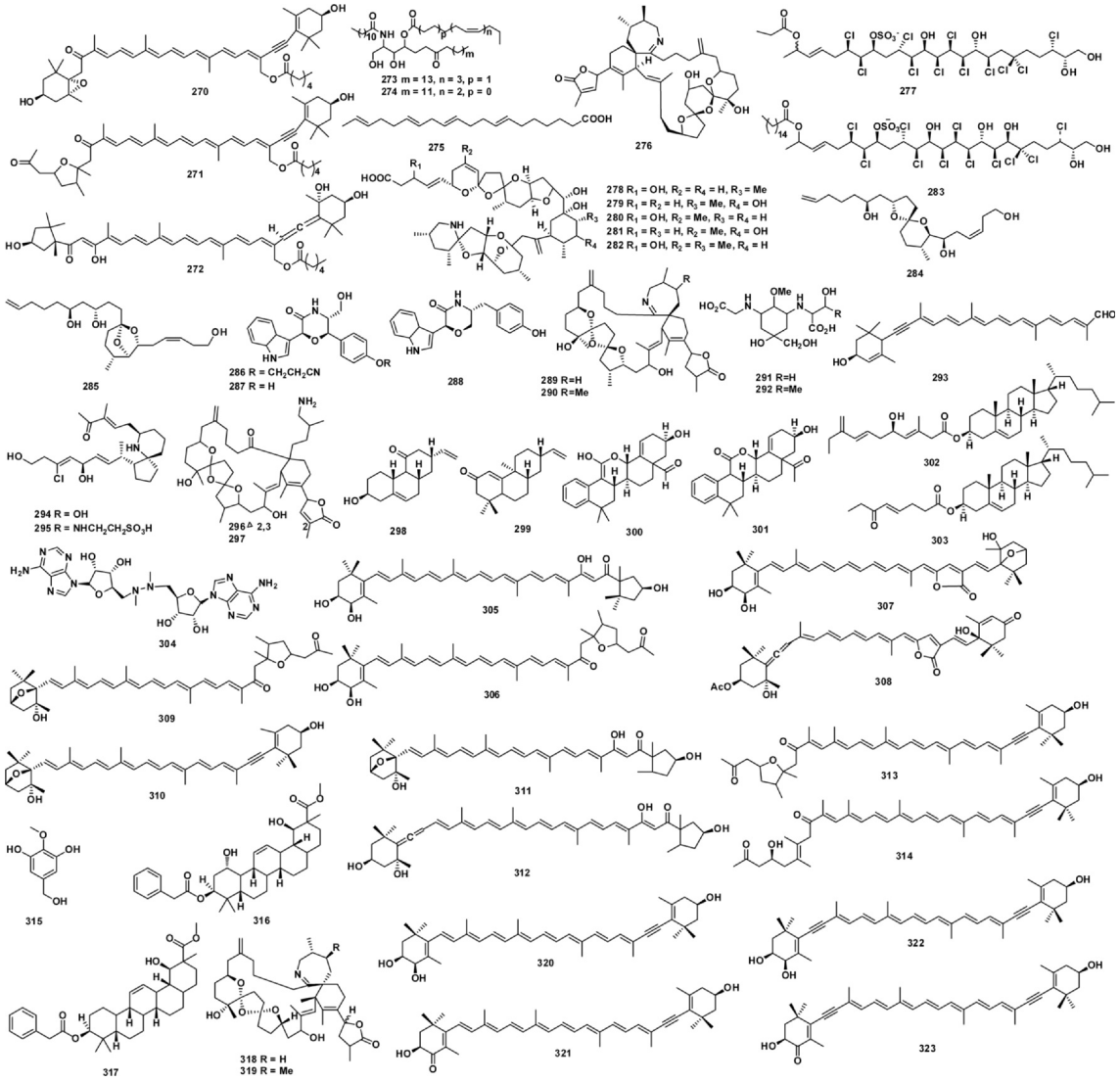


Fig. 11. Structures of compounds isolated from bivalve mussels and oysters. **270–272** Carotenoids, **273–274** Bathymodiolamides A-B, **275** 7, 11, 14, 17-Eicosatetraenoic acid, **276** 20-Methyl spirolide G, **277** Chlorosulfolipid, **278–282** Azaspiracid analogs, **283** Polychlorinated sulfolipid, **284–285** Attenols A-B, **286–288** Oxazinins 1–3, **289–290** Spirolides B-C, **291–292** Mytilin A-B, **293** Apoalloxanthinal, **294** Pinnaic acid, **295** Tauropinnaic acid, **296–297** Spirolides E-F, **298–299** Dodecahydro-phenanthrenone, **300–301** Benzo[*h*]naphtho[1,2-*c*]chromene derivatives, **302–303** Sterols, **304** Ostrerine A, **305–312** Carotenoids, **313–314** Crasssostreaxanthin A-B, **315** 3, 5-Dihydroxy-4-methoxybenzylalcohol, **316–317** Phenylacetyloxy-trimethylpicene-23-carboxylate derivatives, **318** Spirolide B, **319** Spirolide D, **320** Pectenol, **321** Pectenolone, **322** 4-Hydroxyalloxanthin, **323** 4-Ketoalloxanthin.

4-hydroxyalloxanthin **322** and 4-ketoalloxanthin **323** were reported from the scallops (Faulkner, 2000).

7. Chemical classification of secondary metabolites from molluscs of marine and estuarine origin

Marine and estuarine molluscs were endowed with varying classes of organic compounds classified under different categories, particularly as sterols, terpenes, alkaloids, peptides, polypropionates, fatty acids etc. with potential pharmacological properties (Blunt et al., 2007, 2009, 2018, Blunt et al., 2012, 2013, 2014, 2015, 2016, 2017, Blunt et al., 2003, 2004, 2005, 2006, 2008, 2010, 2011; Carroll et al., 2019; Faulkner, 1984, 1986, 1987, 1988, 1990, 1991, 1992, 1993, 1994, 1995, 1997, 1998, 2000, 2002). The comparison of chemical diversity of the major types of secondary metabolites from the bivalves and gastropods were shown in Fig. 12. In gastropods, the terpene class of compounds were dominated by 55% and the sterols were least reported of about 3% (Benkendorff, 2010). However, the sterols were found to occupy the major share of about 41% in bivalves, whereas the terpenes were found to be least reported of about 5% (Benkendorff, 2010). Terpenes were the major area of research of gastropods, which might be attained through their diet for use against defense mechanisms (Stebbings, Gray, Schneiders, & Sansom, 2017). Greater number of sterols in the bivalve molluscs might be due to the biochemical changes in their reproductive pathways (Benkendorff, 2010). Comparatively large numbers of alkaloids (5–6%) and polyproprionates (13–32%) were reported from the molluscs, whereas nitrogenous compounds were relatively rare (Benkendorff, 2010). Extensive reports of secondary metabolites were detailed under each class of molluscs, and herein we have represented some of the important organic classes of molluscan metabolites.

7.1. Terpenes

Marine and estuarine molluscs were described to produce a wide array of variants of intereseting terpenoid metabolites, which were mainly classified under chamigrene, amphilectane, cembrane with unusual functionalities, including groups like isothiocyanates,

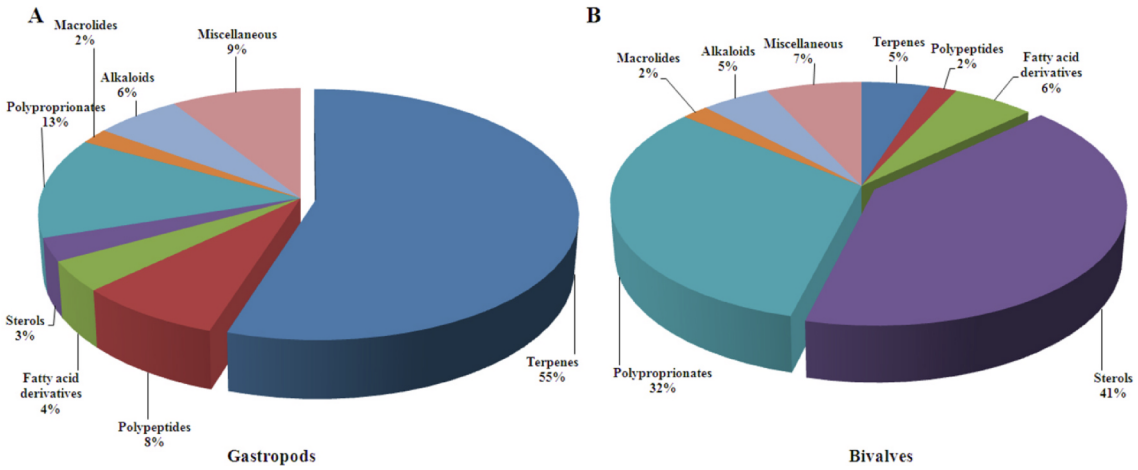


Fig. 12. Relative proportion of the various chemical classes of secondary metabolites isolated from (**A**) gastropods and (**B**) bivalves over the period 2000 to 2019 (compiled from Faulkner, 2000 to 2002; Blunt et al., 2003 to 2018; Benkendorff, 2010; Carroll et al., 2019).

dichloroimines, isonitriles, isocyanates, halogens (Gross & Konig, 2006). The terpenoids from marine molluscs were reviewed from the year of 1984 (Blunt et al., 2007, 2009, 2018, Blunt et al., 2012, 2013, 2014, 2015, 2016, 2017, Blunt et al., 2003, 2004, 2005, 2006, 2008, 2010, 2011; Carroll et al., 2019; Faulkner, 1984, 1986, 1987, 1988, 1990, 1991, 1992, 1993, 1994, 1995, 1997, 1998, 2000, 2002). In most of the cases, the chemical defenses by utilizing the terpenoids might fail to prevent the feeding by certain predators (Gross & Konig, 2006). The mollusc, *A. dactylomela* was known to produce different structural types of terpenes, which were produced through their algal diet (Wessels, Konig, & Wright, 2000). Comprehensive biosynthetic analyses of terpenoids from the marine molluscs were previously carried out (Gross & Konig, 2006). The studies demonstrated that the mollusc produces terpenes not only from their diet, but also by the *de novo* biosynthesis, which includes the degraded sesterterpenes from the mevalonic acid pathway (Fontana et al., 2003a, 2003b; Gavagnin et al., 2001). Biogenesis of diterpenoid glycerides, verrucosins from mollusc *D. verrucosa*, and detailed terpene biosynthesis in *Doriopsilla areolate* were previously reported (Chioccara et al., 1979; Maoka, 1997). The European nudibranch *D. areolate* was characterized by a series of defensive sesquiterpenoids, related to drimane and *ent*-pallescensin A (Butler & Capon, 1993). The strucrtures were unique for these opisthobranch molluscs, even though the basic skeletons of these drimane and *ent*-pallescensin were also reported from sponge, *Dysidea* thereby suggesting that the molluscs and the sponge could represent the prey-predator pair (Butler & Capon, 1993). Sesquiterpenes, ascobullins A-B were reported from *A. ulla* (Gavagnin, Mollo, & Montanaro, 2000), and the anti-inflammatory oxygenated terpenoids classified under furanonorditerpenoid, sesquiterpenoid and diterpenoid were reported from *U. duvauceli* (Chakraborty et al., 2019). A drimane sesquiterpenoid was isolated from *C. ramosus* (Chakraborty & Salas, 2019), C19 norditerpenoid, isopimarane derivative was described from *P. malabarica* (Joy & Chakraborty, 2017), and an irregular meroterpenoid with 5-lipoxygenase inhibitory activities was isolated from *V. cyprinoides* (Joy & Chakraborty, 2018c). The pyranoid enclosed irregularly prenylated farnesene compound and C21 prenylated bisabolene-type meroterpenoid were also described from *P. malabarica* (Joy & Chakraborty, 2017).

7.2. Sterols

Sterols are bioactive lipid analogues, and were found to be the main constituents of all marine molluscs, particularly in the bivalve molluscs (Benkendorff, 2010; Goad & Scheuer, 1978). Diverse structural skeletons of steroids were found to exhibit interesting therapeutic properties, such as anti-inflammatory, inhibition of DNA synthesis, immunological effects, cytotoxicity, and other antagonistic activities (Goad & Akihisa, 1997). These significant classes of compounds were described to possess the ability to cross the lipophilic cell membrane, and binds to the steroid receptors to exhibit their complete physiological functionalities (Sultan & Raza, 2005). It was described that the steroids could be biosynthesized in the marine molluscs under unusual ecological surroundings, and was found to be active as self-protective strategies against the invaders (Zhou et al., 2014). Polyoxygenated tetracyclic nucleus with various degrees of unsaturation, steroids with spiro A/B ring system, steroidal alkaloids, atypical side chain substitution, 3β-cholestane esters, steroid-amino acid conjugates, seco-steroids, and bicyclo[4.4.1]/bicyclo[4.3.1] A/B steroids were reported from various mollusc species (Sica, 1980). Anti-inflammatory properties of the diunsaturated C-27 polyhydroxy sterols against pro-inflammatory cyclooxygenases/cytokines were reported from the gastropod, *Trimusculus peruvianus* (Diaz-Marrero et al., 2003). Ketosteroids were isolated from a marine prosobranch mollusc *Onchidiopsis variegate* (Santalova et al., 2007), and an anti-inflammatory lactonic steroid with 1, 10:8, 9-diseecoergostane framework was described from *B. spirata* (Chakraborty et al., 2019). Two unusual Δ^5 sterols, (5*Z*)-24a-homocholesta-5, $24a^1(24a^2)$-dien-3-ol, 27(25 → 23)-*abeo*-(5*Z*)-3-hydroxy-24-isopropyl cholesteno-26, 23-lactone from *C. ramosus* (Chakraborty et al., 2019), 23-*gem*-dimethylcholesta-5-en-3β-ol and (22*E*)-24^1, 24^2-methyldihomocholest-5, 22-dien-3β-ol from *P. malabarica* (Joy, Chakraborty, & Raola, 2017) along with *abeo*-pregnane-type sterol derivative and polyhydroxylated cholestenols from *V. cyprinoides* were reported previously (Joy & Chakraborty, 2018a). A progesterone homolog was purified from the dorid nudibranch *Aldisas maragdina* (Blunt et al., 2003). Uncommon Δ^8 unsaturated methyl and dimethyl sterols were obtained from the Japanese limpet *C. grata* and *C. toreuma* (Blunt, Copp, Keyzers, Munro, & Prinsep, 2014), whereas 9, 11-secosteroid aplysiasecosterol A, along with two novel secosterols were isolated from *A. kurodai* (Blunt et al., 2018).

7.3. Alkaloids

The number of identified molluscan alkaloids was interestingly increased in the recent years due to their promising biological activities. Alkaloids represented a structurally different class of secondary metabolites, and the occurrence of nitrogen was attributed for their bioactivities (Netz & Opatz, 2015). Several alkaloids were isolated from *O. rivularis*, to treat tuberculosis, dizziness, and to reduce inflammation (Ouyang, 2006). Kigoshi, Imamura, Yoshikawa, and Yamada (1990) reported the alkaloids, named as neoaplaminone sulfate,

neoaplaminone, and aplaminone with cyctotoxic properties from the mollusc, *A. kurodai*. Two new alkaloids, halgerdamine and C^2-α-D-mannosylpyranosyl-L-tryptophan were described from *Halgerda aurantiomaculata* (Fahey & Carroll, 2007). The uncommon 1,2,4-oxadiazole skeleton enclosed phidianidines A-B were isolated from *Phidiana militaris* with cytotoxicity against several tumor cells (Carbone et al., 2011). Phidianidine A was reported as a newer chemokine receptor ligand, which inhibited C-X-C motif chemokine 12-induced DNA synthesis, and cell migration (Carbone et al., 2011). The first ergot peptide alkaloid ergosinine, which was found to play defensive role in marine molluscs, was reported from *P. forskalii* (Wakimoto, Tan, & Abe, 2013). DOPA-(2-amino-3-(3′,4′-dihydroxyphenyl)propionic acid) derived pyrrole alkaloids, lamellarins were first isolated from the mollusc, *Lamellaria* sp. (Andersen, Faulkner, He, Duyne, & Clardy, 1985). Thereafter, more than seventy lamellarin derivatives and pyrrole-derived alkaloids were reported (Fan, Peng, Hamann, & Hu, 2008). The 3,4-diarylated pyrrole 2-carboxylic acid ester or amide functionality was found to be major structural subunit of lamellarins. Most of the lamellarins, lukianols, polycitrins, polycitones, storniamides, and ningalins possessed a common structural subunit, and were predominantly isolated from the marine prosobranch molluscs (Cantrell, Groweiss, Gustafson,& Boyd, 1999). These secondary metabolites were reported to exhibit potential bioactivities, such as cytotoxicity (Cantrell, Groweiss, Gustafson, & Boyd, 1999), antitumor (Carroll, Bowden, & Coll, 1993; Reddy, Faulkner, Venkateswarlu, & Rao, 1997), reversal of multi-drug resistance (Boger, Boyce, Labroli, Sehon, & Jin, 1999), antibiotic (Palermo, Brasco, & Seldes, 1996), and antioxidant (Krishnaiah et al., 2004) properties.

7.4. Polypropionates

During the last thirty years, several structurally-diverse polypropionate metabolites were reported from the marine molluscs (Davies-Coleman & Garson, 1998). Most of the marine polypropionates were reported for their pharmacological potentials, such as cytotoxicity, antimicrobial, antifungal, antibiotic and antiviral properties (Davies-Coleman & Garson, 1998). However, there were other polypropionates that were interrelated with their ecological systems, with no pharmacological effects (Davies-Coleman & Garson, 1998). These typical metabolites of molluscs were derived through the condensation of several propionate units (Davies-Coleman & Garson, 1998). The acyclic polypropionates, siphonarienal (aldehyde) (Norte, Fernandez, & Padilla, 1994), siphonarienone, siphonarienedione, and siphonarienolone (Norte et al., 1990) were reported from an opisthobranch gastropod, *S. grisea*, whereas norsiphonarienone and isosiphonarienolone were described from *S. pectinata* (Paul, Zubia, Oriega, & Salva, 1997). An acyclic polypropionate, aglajne-1 was isolated from *B. occidentalis*, which was regarded as chemical-taxonomic marker for marine molluscs in the genus *Bulla*. This compound was reported to exhibit significant antibacterial potentials against *Escherichia coli*, *Serratia marcescens*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Arrieche et al., 2019). Furanone containing compound, aglajne-2 was isolated from *Aglaja depicta* and *B. striata* (Cimino, Sodano, & Spinella, 1987). Two families of ascoglossan molluscs, Stiligeridae and Polybranchiidae were reported as potential sources of polypropionates (Davies-Coleman & Garson, 1998). The 2-pyrone polypropionates were reported from *Cyerce nigricans* (Roussis, Pawlik, Hay, & Fenical, 1990), *A. depicta* (aglajne-3), and *Navanax inermis* (5,6-dehydroaglajne-3) (Cimino et al., 1987; Spinella, Alvarez, & Cimino, 1993). The 4-pyrone polypropionates were reported from the ascoglossan molluscs, *C. nigricans*, *C. cristallina* and *Ercolania funerea*, in which cyercenes A-B were isolated from *C. cristallina* (Vardaro et al., 1991), and 12-norcyercene B, 7-methylcyercene B, and 7-methyl-12-norcyercene B were reported from *E. funera* (Vardaro, Di Marzo, Marin, & Cimino, 1992). Hemiacetal ring-enclosed marine polypropionates were reported from *Siphonaria australis* (Sundram & Albizati, 1992) and *S. denticulata* (compounds were named as denticulatins A-B) (Hochlowski, Faulkner, Matsumoto, & Clardy, 1983). An unusual 2, 4, 6-trioxaadamantane ring framework-enclosed polypropionate, named as muamvatin was reported from *S. normalis* (Roll, Biskupiak, Mayne, & Ireland, 1986). The polypropionates isolated from the skin of *P. membranaceus* along with the acid secretion were found to bear significant functional role in their chemical defense strategies (Ciavatta et al., 1993). Overall, the polypropionates exhibited pronounced pharmacological potencies along with their ecological effects (Davies-Coleman & Garson, 1998).

7.5. Peptides

Peptides are significant class of secondary metabolites with wide spectrum of therapeutic, and nutraceutical pluralities (Cheung, Ng, & Wong, 2015). Molluscs were occupied with a predominant share in the production of peptides with bioactive pluralities (Cheung et al., 2015) exhibiting cardioprotective, antiviral, anticancer, antioxidative, antimicrobial, analgesic, antidiabetic along with neuroprotective properties. Therefore, this class of chemistry attracted the attention in functional food and pharmaceutical fields for use against several diseases (Cheung et al., 2015). Some of the peptides have higher commercial values, whereas few of them were commercialized in the markets, or in the clinical and preclinical pipelines (Cheung et al., 2015). An important amino acid peptide, ziconotide (25 amino acid peptide with three disulfide bonds) from *C. magus* was reported to possess potential analgesic property, which was found to be 1000 times more potent than morphine (Olivera, 2000). Cone snails were considered as valuable resources of active peptides, called as conotoxins, which were consisted of mixture of peptides with short chains of disulfide amino acids (Nakazawa et al., 2000). Earlier studies postulated that the peptides were effective in the treatment of cancer (Shen, Layer, & McCabe, 2000). A linear pentapeptide, dolastatin 10 and depsipeptide dolastatin 15 with promising antiproliferative activities were reported (Pettit et al., 1995). Dursatellanin-P with 60-kDa protein was isolated from the purple ink of *B. leachii* with anti-HIV activity (Rajaganapathi, Kathiresan, & Singh, 2002). The cyclic hexapeptide keenamide A, and dehydroamino-butyric acid-containing peptide, kahalalide possessing potential antitumor activities F were reported (Garcia-Rocha, Bonay, & Avila, 1996; Wesson & Hamann, 1996).

7.6. Macrolides

Macrocyclic ethers or lactones are cyclic systems with more than ten carbon atoms enclosing ether, ester or ketone groups. These were considered as the significant sources of pharmaceutical medications and nutraceuticals with multiple bio-potentials, such as antitumor, antibacterial and antimalarial etc. (Faulkner, 1986). Previous studies reported the presence of natural macrocycles with more than fifty atoms in the ring system, even though 14-, 15-, 16-membered macrocycles were commonly occurred in nature (Blunt et al., 2007). Since the macrocycles were not rigid, they could easily interact with the dynamic protein targets, and thus exhibited potent bioactivities (Huryn & Wipf, 2014). Macrocyclic lactones or polyethers of molluscan origin were found to possess potent anticancer pluralities (Huryn & Wipf, 2014). The macrocyclic compound, aplyronine and its derivatives, aplyronines B-C were reported from *A. kurodai*, with potent antitumor effects (Yamada, Ojika, Ishigaki, & Yoshida, 1993). Similarly, ichthyotoxic macrolides, aplyolides B-E were found from *A. depilans* (Faulkner, 1995). Stereochemistry of macrocyclic metabolite, ulapualide A from *H. sanguineus* was recognized by total synthesis (Faulkner, 1992). The cephalopod, *A. neglectus* was reported to contain four cardioprotective macrocyclic lactones, which were characterized as 7-hydroxy-5-methyl-1,4-dioxecan-10-one, furo[1,4,8]trioxacyclohexadecine-12,19-dione, octahydro-benzo[1,15]dioxacyclotridecin-2-one and 7-ethyl-octahydro-11-hydroxy-2-oxobenzo[1,12] dioxecine (Chakraborty et al., 2019a). A 16-membered polyether macrocyclic lactone was reported from *B.*

Table 5
Pharmaceutical potential of prominent members of molluscan species against various diseases

Studied mollusc	Common name	Bioactivities	References
Arca subcrenata	Ark clam	Anti-inflammatory activity by inhibition of NO generation in LPS-stimulated RAW264.7, reduced production of IL-8, inhibition of COX-2 and *i*NOS pathways	Wu, Hu, Song, Zhu, & Yu, 2014
Bellamya bengalensis	Snail	Anti-inflammatory activity by inhibition of ROS, TNF-α and NO generation, inhibition of NF$\kappa\beta$ translocation	Bhattacharya et al., 2014
Buccinulum corneum	Snail	Antiviral activity against human T-cell leukemia virus-1	Orlando et al., 1996
Crenomytilus grayanus	Mussel	Antiviral activity against HIV virus	Luk'yanov et al., 2007
Perna canaliculus	New Zealand green-lipped mussel	Antioxidant, anti-inflammatory activity by inhibition of PGE_2 generation, inhibition of lipoxygenase, antihypercholesterolemia, TNF-α and PGE biosynthesis, inhibition of TNF-α and IL-1 generation, inhibition of COX-1 and COX-2	Halpern, 2000
Aplysia fasciata, Aplysia punctate	Sea hare	Reduction in NO concentration, anti-inflammatory activity by inhibition of LOX	Pereira, Taveira, Valentao, Sousa, & Andrade, 2015
Mytilus unguiculatus	Mussel	Anti-inflammatory activity, reduction in swelling associated with paw edema, suppression of inflammatory mediators and pro-inflammatory cytokines	Khan & Liu, 2019
Paphia malabarica	Clam	Antioxidant activities against free radicals, anti-inflammatory activity against COX-1, COX-2 and 5-LOX, antidiabetic activities, ACE-1 inhibition	Joy & Chakraborty, 2017a
Sepia officinalis	Cuttlefish	Inhibition of acetic acid-induced writhing, increase in latency period of mice in hotplate	Fahmy & Soliman, 2013
Sepia pharaonis	Cuttlefish	Anti-inflammatory activity, reduction in carrageenan-induced and formalin-induced paw edema, ACE-1 inhibitory activity	Joseph et al., 2005; Chakraborty, Joy, & Vijayagopal, 2016
Coelatura aegyptiaca	Mussel	Reduction in paw licking, slight increase in latency time of mice in hotplate	Fahmy & Soliman, 2013
Perna viridis	Green mussel	Anti-inflammatory, reduced histamine-induced edema, significant reduction in carrageenan-induced edema, inhibition of dextran-induced paw edema, antioxidant	Chakraborty et al., 2014, 2016
Rapana venosa	Whelk	Respiratory syncytial virus, antiviral activity against Herpes	Nesterova et al., 2011; Dolashka et al., 2016
Haliotis discus	Abalone	Inhibition of NO production in RAW264.7, reduction in TNF-α and IL-6 concentration, suppression of NO production through *i*NOS, reduction in TNF-α , IL-6 generation	Joung et al., 2014
Cistopus indicus	Octopus	Anti-inflammatory activity against COX-1, COX-2 and 5-LOX, antidiabetic activities against α-amylase and DPP-4	Chakraborty, Joy, Raola, & Makkar, 2017
Babylonia spirata	Gastropod	Antioxidant, anti-inflammatory, antidiabetic activities	Salas & Chakraborty, 2020
Chicoreus ramosus	Gastropod	Antioxidant activities against free radicals, anti-inflammatory activity against COX-1, COX-2 and 5-LOX, antidiabetic activities	Salas & Chakraborty, 2020
Haliotis diversicolor	Abalone	Anti-inflammatory activity by reduction in *i*NOS manifestation, augmentation of macrophage function	Chen et al., 2016
Villorita cyprinoides	Clam	Anti-inflammatory activity against COX-2	Joy & Chakraborty, 2018b
Haliotis laevigata, Haliotis rubra	Abalone	Antiviral activity against Herpes	Dang, Benkendorff, & Speck, 2011
Littorina littorea	Periwinkle	Antiviral activity against Herpes	Defer, Bourgougnon, & Fleury, 2009
Helix lucorum	Snail	Antiviral activity against Epstein-Barr virus	Zagorodnya, Dolashka, Baranova, Golovan, & Nesterova, 2011
Sepia inermis	Cuttlefish	ACE-1 inhibitory activity, antidiabetic activities of inhibition of α-amylase and dipeptidyl peptidase 4 enzymes	Krishnan & Chakraborty, 2019
Mercenaria mercenaria	Clam	Antiviral activity against leukaemia viruses	Judge, 1966
Crassostrea madrasensis	Oyster	*In vitro* anti-inflammatory activities against COX-2, 5-LOX, antihypercholesterolemic activity against HMGCR, antihypertensive activity against ACE-1, antidiabetic effects against α-amylase, α-glucosidase, DPP-4, free radical inhibition	Krishnan & Chakraborty, 2019
Crassostrea gigas, Crassostrea rhizophorae	Oyster	Antiviral against Herpes, infectious pancreatic necrosis virus, human adenovirus	Carriel-Gomes, Kratz, Muller, Barardi, & Simoes, 2006; Prescott, Li, Caldes, & Martino, 1966
Amphioctopus marginatus	Octopus	Antioxidant activity, antihypertensive activity against ACE-1, inhibition of HMGCR	Krishnan & Chakraborty, 2019
Uroteuthis duvauceli	Loligo	*In vitro* anti-inflammatory activities against COX-2, 5-LOX, antihypercholesterolemic activity against HMGCR, antihypertensive activity against ACE-1, antidiabetic effects against α-amylase, α-glucosidase, DPP-4, free radical inhibition	Krishnan & Chakraborty, 2019

COX – Cyclooxygenase; LOX – Lipoxygenase, ACE-1 – Angiotensin converting enzyme, IFN – Interferon, NO – Nitric oxide, LPS – Lipopolysaccharide, IL – Interleukin, *i*NOS-Inducible nitric oxide synthase, ROS – Reactive oxygen species, TNF-α – Tumor necrosis factor alpha, HIV – Human immune deficiency, PGE – Prostaglandins, DPP-4 – Dipeptidyl peptidase 4, HMGCR – 3-Hydroxy-3-methylglutaryl-CoA reductase

spirata with anti-inflammatory potential (Salas & Chakraborty, 2018a).

7.7. Fatty acids

Lipids and fatty acids, which were found to be essential for the formation of membrane structures, and their metabolic activities, were the key pre-structures of biological membranes of molluscs (Hadfield & Paul, 2001). The fatty acids DHA and EPA were reported to be biosynthesized by the dinoflagellates and diatoms, and were ubiquitous in the molluscs of marine origin. The diet components and feeding mechanism were the key factors to cause changes in the type, and amount of fatty acid production in molluscs (Hadfield & Paul, 2001). For example, the diet of filter feeder bivalves includes dinoflagellates that were reported to possess higher levels of DHA (Iijima, Kisugi, & Yamazaki, 2003), whereas the detritus feeder molluscs were reported for higher levels of saturated and mono-unsaturated fatty acids (Jansen & de Groot, 2004). Variation in the composition of PUFAs in the molluscs might be due to the transport of fatty acids to their reproductive

organs for development of gonad. For example, winter is the reproductive time of molluscs, and therefore, the fatty acid level could be lower in this season (Bachere, 2003). Also, temperature, metabolic rate, physiological activities, and food availability could significantly affect their fatty acid production (Bachere, 2003). Fatty acids, neutral lipids, phospholipids, odd-numbered fatty acids and C20 polyunsaturated fatty acids were previously reported from the mollusc (Benkendorff, Davis, Rogers, & Bremner, 2005). Derivatives of fatty acids along with other secondary metabolites were characterized from the sea hare *A. kurodai* (Benkendorff, 2010). Previous reports inferred that palmitoleic, oleic, linoleic and arachidonic acids from molluscs possessed potential antimicrobial properties against the human pathogens (Benkendorff et al., 2005). Overall, the fatty acids might contribute towards the maintenance of cell membrane and reproductive cycle of molluscs (Benkendorff et al., 2005). A polyunsatrated fatty acid, namely heneicosa-5, 8, 11, 14-tetraenoic acid was reported as a novel natural product from the mollusc, *S. lignarius* (Blunt, Copp, Keyzers, Munro, & Prinsep, 2013).

7.8. Miscellaneous

Compounds with mixed biosynthetic origin do not fall into any class of organic chemistry, which were described herein. The alarm pheromones, named as alkyl phenols from the bubble snail *Haminoea callidegenita* (Faulkner, 1998) and an unusual chlorinated pyrrolidone *Asteronotus cespitosus* (Blunt et al., 2013), were classified as miscellaneous metabolites. A diacylguanidine, limaciamine was obtained from *Limacia clavigera* (Faulkner, 1998). The metabolite, aplysiaviolin from *Aplysia parvula* (Blunt et al., 2013) and a *trans*-decalin from the limpet, *Trimusculus reticulatus* (Blunt et al., 2006), were reported. Antimicrobial brominated indoles, along with indolequinones were reported from *Drupella fragum* (Faulkner, 1998). A series of malyngamide metabolites with mild cytotoxicity and anti-inflammatory potential were reported from *B. leachii* (Blunt et al., 2006). The C15-halogenated compounds and dihydrocaulerpenynes were reported from *A. dactylomela* and *E. expansa*, respectively (Faulkner, 1998). The polyol, durinskiol A from *Chelidonura fulvipunctata*, mycosporine-like amino acids, aplysiapalythine A-C from *A. californica*, cytotoxic isonitrile-containing lipid, actisonitrile from *A. papillatus*, phorboxazole related metabolites from the Indian nudibranch, *Aldisa andersoni* were also classified as miscellaneous (Blunt et al., 2006; 2007; 2008; 2009; 2010; 2013; 2014; 2015; 2016; 2017; 2018). Chromenoids/isochromenoids from *S. inermis* (Krishnan et al., 2019), isochromenone/furano-chromene derivatives from *P. malabarica* (Joy & Chakraborty, 2017) and pyranoids/isochromenoids/spirocyclic ethers from *V. cyprinoides* (Joy & Chakraborty, 2018c; 2018b) with anti-inflammatory, antioxidative, and anti-hyperglycemic potentials were previously described.

8. Pharmacodynamic studies and therapeutic applications of marine and estuarine molluscs

The unfavorable living conditions and the defensive mechanisms of the marine or estuarine molluscs were found to produce compounds with pharmacological potentials against various diseases (Table 5). Comparison of number of reports on various pharmacological properties of major molluscan species, such as *H. diversicolor*, *H. discus*, *B. spirata*, *B. zeylanica*, *Bursa spinosa*, *C. ramosus*, *P. malabarica*, *V. cyprinoides*, *M. meretrix*, *P. viridis*, *P. canaliculus*, *C. madrasensis*, *L. duvauceli* (*U. duvauceli*), *C. indicus*, *S. pharaonis*, *S. inermis* and *A. marginatus* (retrieved from the Google Scholar excluding citations and patents, accessed on 12/10/2019) were illustrated in Fig. 13. These reports described that about 23% of pharmacological properies were exhibited by *H. discus* followed by *P. viridis* (20%), *M. meretrix* (15%), *H. diversicolor* (12%), and *P. canaliculus* (9%), in the descending order.

8.1. Antioxidant activity

Several molluscs were reported for their various antioxidant pluralities. Polysaccharides from *Mactra chinensis* were reported to possess scavenging activities against hydroxyl and superoxide anion free radicals (Lin-rui, Qing, Zhen-Xing, Yu-Chao, & Lin, 2012). Aqueous and alcoholic extract of *M. veneriformis* showed *in vitro* antioxidant potentials (Luan, Wang, Wu, Jin, & Ji, 2011). It was stated that the presence of hydrophilic/lipophilic antioxidant components like PUFAs, amino acids and carotenoids were accountable for the functional food and therapeutic potentials of the molluscs (Luan, Wang, Wu, Jin, & Ji, 2011). There were reports for the occurrence of antioxidants in molluscs that could constrain the cell damages from oxidative reactions (Nagash et al., 2010). Abalone (gastropod mollusc) extracts were reported to possess prospective antioxidant and anticoagulant properties (Kim et al., 2006). Dose-dependent antioxidant responses of the methanolic extracts of *P. malabarica* and its lipid peroxidation inhibition potentials against the reactive oxygen species were reported in an earlier study (Pawar, Nagvenkar, & Jagtap, 2013). Studies on bivalve mollusc, *P. viridis* highlighted the potential antioxidant activities related to the free radical inhibition and lipid peroxidation, and thus inferred its utilities as prospective health food (Chakraborty et al., 2016). The enzymatically obtained gelatin hydrolysate of flying squid displayed potent antioxidant ability through 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical quenching mechanism at the concentrations of 16 and 12 mg/mL. This inhibotry activity was found to superior than the synthetic antioxidants like butylated hydroxyanisole and α-tocopherol. The gelatin hydrolysate was found to contain antioxidant amino acids, such as histidine, proline, tyrosine, leucine and alanine (Suarez-Jimenez, Burgos-Hernandez, & Ezquerra-Brauer, 2012). The studies showed that the hydrolysate with molecular weight of 383–1492 Da and the presence of aromatic and hydrophobic amino acids, were considered as the predominant reasons for its potential antioxidant activities. Hydrophobicity of the compounds was reported to play a significant role for their antioxidant properties owing to an increased accessibility to the hydrophobic target sites (Suarez-Jimenez et al., 2012). *In vitro* antioxidant property of *P. viridis* was ascribed to the presence of phenolic compounds that could act as hydrogen or electron donors. The abilities to delocalize the unpaired electrons, and the chelation of metal ions were attributed by their antioxidant potentials (Sreejamole & Radhakrishnan, 2013).

Antioxidant potencies of the crude extracts of cephalopods, such as *S. pharaonis*, *U. duvauceli*, *C. indicus*, *S. inermis* and *A. marginatus* were previously reported (Chakraborty & Joy, 2017; Chakraborty et al., 2017). These established that the greater total phenolic contents in molluscs might play an important role in inhibiting the free radicals, and the total phenolic contents were positively correlated with their antioxidant activities (Chakraborty et al., 2017; Moncheva et al., 2004). Potential radical scavenging activities of *C. indicus* and *S. inermis* might be due to the presence of substituted oligosaccharide fractions with hydroxyl groups and unsaturations. These could effectively donate the protons to the free radical by hydrogen atom transfer mechanism (Chakraborty et al., 2017). Methanol and ethyl acetate tissue extracts of *Littorina littorea* (Borquaye, Darko, Oklu, Anson-Yevu, & Ababio, 2016) and the ink extract of *S. officinalis* displayed antioxidant potentials (Soliman, Fahmy, & El-Abied, 2015). Antioxidant potentials of tissues and ink extracts of the cephalopods were detailed in a previous report of literature (Choi, Kim, & Kim, 2015). The historical seafood, *M. meretrix* was found to harbor antioxidant pluralities (Wei, Lin, Niu, & Li, 2007). Aqueous and ethanolic extracts of New Zealand surf clams, *Crassula aequilatera*, *Mactra murchisoni*, and *Paphies donacina* were found to possess potential antioxidant properties (Odeleye et al., 2016). Bioactive components, such as peptides, proteins, and enzyme inhibitors identified from *M. meretrix* exhibited antineoplastic and antioxidant effects (Huang et al., 2005; Zhao, Gao, & Su, 1992). Chakraborty, Joseph, and Chakkalakal (2014) studied the effect of

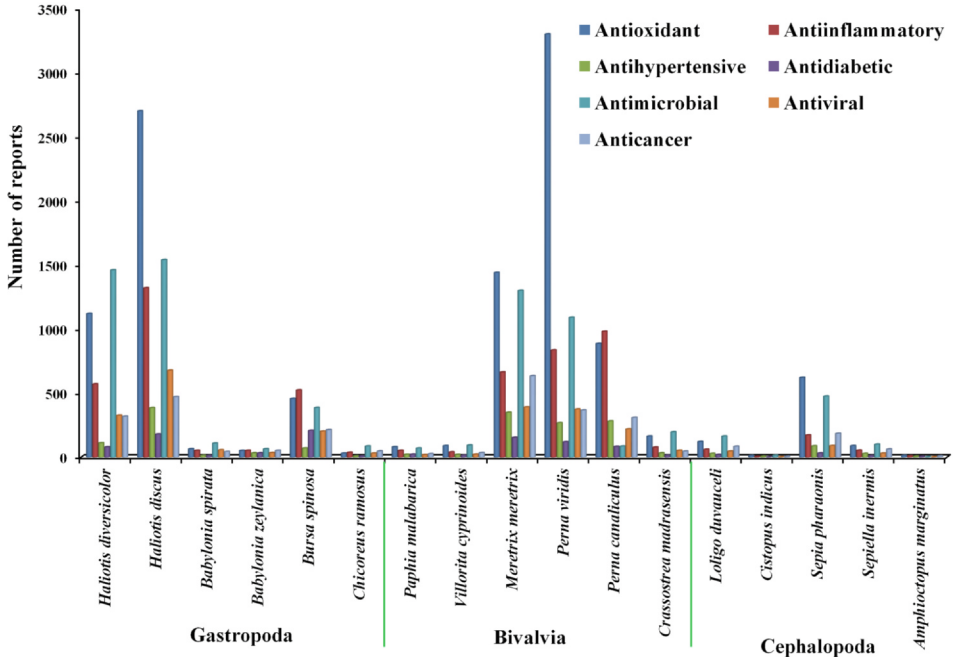


Fig. 13. Comparison of number of reports on various pharmacological properties of major mollusc species (retrieved from Google Scholar excluding citations and patents, accessed on 12/10/2019).

natural additives on fatty acid signatures of *P. viridis* in time-dependent accelerated shelf-life study, and studied the antioxidative status of a nutrient-enriched formulation through a shelf-life study (Chakraborty et al., 2016).

8.2. Anti-inflammatory activity

Extract of the Australian muricid gastropod, *D. orbita* was found to exhibit nutraceutical functionalities and anti-inflammatory properties through inhibition of prostaglandin E_2 (PGE_2), tumor necrosis factor alpha (TNFα), and nuclear factor kappa-β (Ahmad et al., 201). Higher C_{20}-C_{22} *n*-3 fatty acid contents present in the cephalopod species were found to be accountable for their anti-inflammatory activities (Russo & Tringali, 1983). Ink extract of *S. officinalis* displayed anti-inflammatory potentials (Soliman et al., 2015). Anti-inflammatory activity of mussel, *Coelatura aegyptiaca* was evaluated by Fahmy and Soliman (2013), whereas the methanol, ethanol, and aqueous extracts of *P. viridis* exhibited anti-inflammatory properties in different *in vivo* models (Sreejamole, Radhakrishnan, & Padikkala, 2011). Earlier studies of freeze-dried extract of New Zealand green-lipped mussel *P. canaliculus* exhibited the capacity to prevent the induced inflammation. It could act as dual inhibitors of membrane arachidonic acid oxygenation by cyclooxygenases and lipoxygenase mechanisms, thereby decreasing the synthesis of prostaglandin, and leukotriene along with the down-regulation of inflammatory pathways (Bierer & Bui, 2002). C_{20}-C_{22} *n*-3 PUFAs, namely EPA and DHA were regarded as the precursors of anti-inflammatory resolvins, E- and D-series, which were found to be higher in *P. viridis* (Al-Nouri, Al-Khalifa, & Shahidi, 2012). The bivalve mollusc, *P. canaliculus* was used against osteoarthritis and rheumatoid arthritis (McPhee et al., 2007). The Asian green mussel *P. viridis* was found to exhibit potent *in vitro/in vivo* anti-inflammatory effects (Chakraborty et al., 2014), wherein the role of green mussel extract supplemented with natural antioxidant additives on inflammatory prostaglandins, $PGE_2/PGF_{2\alpha}$ and C20 *n*-6 fatty acid were studied through accelerated shelf-life study. This study highlighted the use of PGE_2 and $PGF_{2\alpha}$ analyses as an index of lipid peroxidation, and antioxidant potentials (Chakraborty et al., 2014). Carrageenan-induced edema model was used to check the efficacies of green-lipped mussel extract, which showed significant relief from foot-pad edema in rats (Khan & Liu, 2019). The arthritic rats were effectively cured by furan-fatty acids obtained from the green-lipped mussel (Wakimoto et al., 2011). The Okinawan mollusc, *Pinna muricata* was reported for Ca^{2+} channel activation, and was found to possesses anti-inflammatory properties (Murphy, Mooney, Mann, Nichols, & Sinclair, 2002). Aryl polyketides isolated from *P. malabarica* exhibited greater anti-inflammatory properties against 5-lipoxygenase enzyme (IC_{50} 0.76–0.92 mg/mL), when compared to the standards, sodium salicylate (IC_{50} 1.75 mg/mL) and ibuprofen (IC_{50} 0.93 mg/mL) (Joy & Chakraborty, 2017d). The 1*H*-benzochromenone compound from *C. ramosus* exhibited greater inhibitory activity against 5-lipoxygenase enzyme (IC_{50} 2.12 mM), when compared to the standard (Chakraborty & Salas, 2019; Chakraborty & Salas, 2019b). A polysaccharide, namely glycosaminoglycan-xylopyranan from *B. spirata* was reported to attenuate pro-inflammatory 5-lipoxygenase (Chakraborty, Krishnan, & Joy, 2019). Anti-inflammatory 2*H*-chromenyl derivatives were isolated from the organic extract of *B. spirata* (Chakraborty & Salas, 2020). A polygalactosamino-glucopyranosyl fucopyranose isolated from C. *madrasensis* exhibited prospective anti-inflammatory activities against pro-inflammatory enzymes COX-2 and 5-LOX ($IC_{50} \leq 0.16$ mg mL^{-1}). Quantitative real-time polymerase chain reaction displayed that the polygalacatan suppressed the mRNA of nuclear factor-κB and COX-2 in lipopolysaccharide-induced macrophages (Chakraborty, Krishnan, & Joy, 2020).

8.3. Antihypertensive activity

Consumption of molluscs and its related products were reported with a number of health benefits, particularly as antihypertensive agents. For example, noteworthy reductions in the pathophysiologies related to hypertension were found to be associated with the consumption of blue mussels and oysters due to the occurrences of biologically active peptides (Wijesekara & Kim, 2010). The trypsinized hydrolysate peptide with the sequence of Trp-Pro-Met-Gly-Phe (molecular weight of 636.75 Da), which was described from the clam, *Cyclina sinensis*, was reported for antihypertensive activity against angiotensin converting enzyme (ACE) in a competitive manner with an IC_{50} value of

0.789 mM (Yu et al., 2018). This studied peptide, which has hydrophobic amino acid residues at C-terminus, and N-terminus, was considered as the significant characteristic for prospective ACE inhibitory activity (Yu et al., 2018). Its molecular docking simulation inferred that this peptide could bind to active site of ACE, and the conformation of pentapeptide-ACE complex was stable (Yu et al., 2018). A macrocyclic lactone with furo[1,4,8]trioxacyclohexadecine-12,19-dione from *A. neglectus* was reported to exhibit potent *in vitro* ACE inhibition with IC_{50} of 1.12 mM, and also revealed its protecting effects against angiotensin-II induced cardiac hypertrophy on H9C2 cells at 25 μg/mL (Chakraborty et al., 2019a). The latter study found around 34% decrease in the cell area, together with increase in viability attributed to its antihypertrophic effects and enhanced regeneration of cardiomycetes (Chakraborty et al., 2019a). A noteworthy reduction of about 86.8% in cellular size of H9C2 cells upon macrocyclic lactone treatment, appropriately confirmed its potential to inhibit ACE-II induced cardiac hypertrophy (Prathapan, Vineetha, Abhilash, & Raghu, 2013). *In vitro* antihypertensive properties of the organic extracts of *S. pharaonis*, *U. duvauceli*, *C. indicus*, *S. inermis* and *A. marginatus* were studied using the proton-nuclear magnetic resonance spectroscopic techniques (Chakraborty et al., 2017). Antihypertensive components were reported from the squids, cuttlefish, and octopus (Balti et al., 2015). The muscle protein hydrolysates of mollusc were reported for antihypertensive potential against ACE-I (Tsai, Chen, & Pan, 2008). Antihypertensive peptides from *Mytilus coruscus* was reported in the earlier literature (Wu, Cheng, & Shi, 2013). The peptides and proteins isolated from *M. meretrix* exhibited potential antihypertensive as well as antineoplastic effects (Wei et al., 2007). A sulfated *N*-acetylglucosamino glucuronopyranosyl-arabinopyranan isolated from seafood *Amphioctopus neglectus* displayed potential angiotensin converting enzyme attenuation properties. This sulfated polysaccharide was reported to attenuate angiotensin-II induced cardiac hypertrophy of the cardiomyoblast cells (Chakraborty, Krishnan, & Joy, 2020).

8.4. Antidiabetic activity

Previous reports of literature described that the antidiabetic potencies of the cephalopod molluscs were greater than those exhibited by the gastropods and bivalves (Tiwari et al., 2008). Potent antidiabetic effect of *C. indicus* extract was particularly due to its dipeptidyl peptidase-IV inhibitory property (Chakraborty et al., 2017). Organic extract of *C. indicus* inhibited the degradation of glucose-dependent insulinotropic polypeptide and glucagon-like peptides (incretins) to enhance the generation, and the release of insulin from pancreatic *β*-cells (Kim et al., 2011). Therefore, it is of note that the inhibition of dipeptidyl peptidase-IV was important for an effective maintenance of serum glucose levels, and thus the activities of endogenous incretins were preserved (Kim et al., 2011). The bivalve clams, *P. malabarica* and *V. cyprinoides* exhibited *in vitro* antidiabetic potential against the carbolytic enzymes and dipeptidyl peptidase-IV with IC_{50} (inhibitory concentration at 50% inhibition) values of 1.39–1.54 and ~ 1.04 mg/mL, respectively (Joy, Chakraborty, & Pananghat, 2017). Methanol extract of *Cerithidea obtuse* (snail) was composed of alkaloids, terpenoids, and flavonoids with potential antidiabetic property (IC_{50} value of 36.40 mg/mL) (Cahyani, Purwaningsih, & Azrifitria, 2015). An isochromenyl derivative isolated from *S. inermis* exhibited efficient inhibition of carbolytic (IC_{50} 0.19–0.28 mg/mL) and dipeptidyl peptidase-IV enzymes (IC_{50} 0.16–0.23 mg/mL) (Krishnan, Chakraborty, & Joy, 2019). An antioxidant 1*H*-benzochromenone reported from *C. ramosus* displayed greater inhibitory activity against the carbolytic enzymes (IC_{50} ~ 0.72 mM) when compared to the standard acarbose (IC_{50} 0.43 mM) (Chakraborty & Salas, 2019; Chakraborty & Salas, 2019b).

8.5. Antimicrobial activity

Marine and estuarine molluscs were identified as untapped resources of several antimicrobial compounds, including indole alkaloids, chlorinated acetylenes, peptides, and glycol proteins (Zhong, Wang, Yang, Yan, & Liu, 2013). Among these, antimicrobial peptides were shown to be an important class of host defensive system of many molluscs, and the presence of polysaccharides, especially sulfated muco-polysaccharides were also attributed to their antimicrobial potentials (Dolashka et al., 2016). These species used their innate immunity to get along with the invading microbial pathogens due to the lack of a well-defined defensive system. To date, an approximate number of 69 peptides with antimicrobial properties were described from the bivalves and gastropods (Li, Parisi, Parrinello, Cammarata, & Roch, 2011). Antimicrobial activity was reported from the mucus of giant snail *Achatina fulica*, in which the highest potency was reported against *Escherichia coli*, and the lowest against *Klebsiella oxytoca* (Dolashka et al., 2016; Kubota et al., 1985). Crude ethanol extract of gastropod, *B. spirata* exhibited pronounced antimicrobial property against wide range of bacterial and fungal strains (Periyasamy, Srinivasan, & Balakrishnan, 2012). It was reported that the steroids extracted from mollusc, *M. meretrix* displayed potential inhibition of cell growth, along with induction of G1-phase cell cycle arrest in the hepatoma cells (Wu et al., 2006). Bactericidal proteins from the littoral mollusc *Cenchritis muricatus* with antibacterial property, was reported previously (Lopez-Macia, Jimenez, Royo, Giralt, & Albericio, 2001). Protein extract from the gastropod, *Cryptozona bistrialis* was found to be capable of inhibiting various pathogenic microorganisms (Ulagesan & Kim, 2018). Arenas, Guzman, Cardenas, Mercado, and Marshall (2009) described the antifungal activity of polyproline-type antimicrobial peptides (47 residues) from the Chilean scallop, *Argopecten purpuratus* against *Fusarium oxisporum* and *Saprolegnia parasitic.* Hemocyanins isolated from the hemolymph of *H. aspersa* showed prospective antimicrobial properties against Gram-positive pathogen *Streptococcus epidermidis* and Gram-negative *E. coli* (Dolashka et al., 2016). Antibacterial and antifungal potentials of *B. spirata*, *P. glaucum*, *T. dolium*, *Hemifusus pugilinus*, *C. ramosus* and *B. zeylanica* collected from the southeast coast of India were investigated previously (Jayanthi, Anand, Chelladurai, & Kumaraguru, 2016). The abalone exhibited *in vitro* and *in vivo* antibacterial properties (Vakalia & Benkendorff, 2005). Antimicrobial activities of gill extract from the bivalve, *P. viridis* (Chandran, Rameshkumar, & Ravichandran, 2009) and crude solvent fractions of the marine clam, *Anadara granosa* and *M. casta* against pathogenic bacteria were reported (Ramasamy & Balasubramanian, 2012, 2014). Previous and on-going investigations disclosed that the mollusc species of marine and estuarine origin were not only an important source of food, but are also promising candidates for development of antibiotic drugs against bacterial and fungal infections.

8.6. Antiviral activity

Marine molluscs were economically viable sources of antiviral compounds due to their extensive ability to fight against viral infections (Khan & Liu, 2019). This was due to the absence of a well-defined adaptive immune system, and these species make use of their inherent immune system as a defense against viral infections (Khan & Liu, 2019). Antiviral properties of the marine and estuarine molluscs were attributed to RNA interference, programmed cell death responses, which were similar to the vertebrate interferon pathway (Green & Montagnani, 2013). Peptides and glycoproteins extracted from the molluscs were the predominant compounds responsible for their antiviral properties (Kubota et al., 1985). Kelletinin A isolated from *Buccinulum corneum* showed prospective bioactivity against the human T-cell leukemia virus type-1 (Orlando, Strazzullo, Carretta, De Falco, & Grippo, 1996). Defensin and mytilin isolated from *M. galloprovincialis* possessed activity against human immunodeficiency virus type-1 (HIV-1) and white spot syndrome virus, respectively (Dupuy, Bonami, & Roch, 2004; Roch, Yang, Toubiana, & Aumelas, 2008). A lectin derived from *Crenomytilus grayanuss* showed activity against HIV (Luk'yanov

et al., 2007). These compounds were found to interact with the invading virus, and prevent their binding with target cells or inhibit its replication and transcription (Luk'yanov et al., 2007). Hemocyanin 1 and 2 (glycosylated functional part) extracted from *Rapana thomasiana* exhibited antiviral activity against both herpes simplex virus type-1 and Epstein-Barr virus by inhibiting the replication at 200 μg/mL and 1 μg/mL, respectively (Cheung et al., 2014). The abalone was reported to possess antiviral properties against human pathogens, as described by the *in vitro/in vivo* experiments on the infected mice (Li, Prescott, & Jahnes, 1962). Extracts from *P. viridis*, *C. madrasensis*, *C. gryphoides*, *M. casta*, *V. cyprinoides*, and *Polymesoda erosa* were found to possess prospective antiviral activities against influenza virus type-A and type-B (Chatterji et al., 2002). In addition, *P. viridis* was reported for its antimicrobial, radioprotective, antiangiogenic and anti-HIV potencies (Annamalai, Anburaj, Jayalakshmi, & Thavasi, 2007; Mirshahi et al., 2009). The sea hares, *Dolabella*, *Bursatella* and *Aplysia* were found to be the potential sources of anti-HIV metabolites (Yamazaki, 1993). A new polysaccharide bearing galactan sulfate isolated from the clam, *Meretrix petechialis* exhibited anti-HIV activity (Amornrut et al., 1999).

8.7. Anticancer activity

Chemical investigation of the phylum Mollusca described various compounds as potential anticancer drugs based on their ability to overcome the cancer cell resistance chemotherapy (Ciavatta et al., 2016). The reason behind the selection of mollusc-derived anticancer drug candidates were due to their ability to target the biological characteristics of cancer cells, and their potency, selectivity, mechanisms of action along with alimentary behaviour (Ciavatta et al., 2016). Now-a-days, researchers are focused in the identification of peptides as caspase activators, since these were involved in the intracellular and extracellular apoptosis pathways (Zheng et al., 2011). For example, dolastatin-10 derived from *D. auriculata*, and its synthetic analogs were currently passed through phase-II clinical trials, as antitumor agents (Madden et al., 2000). Kahalides showed both *in vitro/in vivo* activities against cancer cells through the inhibition of lysosomal function leading to the cell death (Suarez-Jimenez et al., 2012). Molluscan peptides were found to possess anticancer properties through different mechanisms of action in killing the cancer cells, like inhibition of angiogenesis, apoptosis, and disruption of tubulin-microtubule balance (Kang, Choi, Seo, & Park, 2018). Enzymatic hydrolysate of jumbo squid skin gelatin was found to exhibit cytotoxicity against MCF-7 and U-87 cell lines with IC_{50} values of 0.13 and 0.10 mg/mL, respectively (Chen et al., 2010). The cephalopod species, *Paraoctopus limaculatus* (octopus) was studied for their antimutagenic and antiproliferative effects (Moreno-Felix et al., 2013) Various antitumor metabolites were isolated from the squid (Chen et al., 2010), octopus (Karthigayan, Sri Balasubashini, Sengottuvelan, Balasubramanian, & Somasundaram, 2006), and cuttlefish (Senan, Sherief, & Nair, 2013). Extract of edible clam, *Mercenaria mercenaria* was found to attenuate the development of tumors in the Swiss mice (Schmeer & Huala, 1965).

8.8. Other pharmacological activities

The gastropod snail, abalone was recommended for physically weak patients (Kim et al., 2006). Studies on bioactive properties of mucus from *Helix* sp. revealed its mucolytic, bacteriolytic, antispasmodic properties (Bonnemain, 2005). Anticoagulant properties of abalone extracts were studied previously (Kim et al., 2006). Conopeptides from the cone snails were reported for various biomedical pluralities, such as antinoceptive, analgesic, and as neuroprotectives (Han, Teichert, Olivera, & Bulaj, 2008; Twede, Miljanich, Olivera, & Bulaj, 2009). Recent pharmacological studies on secretions of *C. aspersa* were described for their skin regenerative pluralities through antioxidant activity, stimulation of fibroblast proliferation along with metalloproteinase regulation potencies (Brieva et al., 2008). The cephalopods including squid and octopus have broad physiological actions, such as immune and anti-inflammatory responses, along with neural function and reproduction (Miliou, Fintikaki, Tzitzinakis, Kountouris, & Verriopoulos, 2006). A natural thrombolytic agent, C-type hemolytic lectin was purified from *V. cyprinoides* with activity against myocardial infarction (Sudhakar & Vincent, 2014). The Asiatic hard clam, *M. meretrix* was reported to exhibit several pharmacological activities, such as immunomodulatory, antihyperglycemia, and antihyperlipidemia along with detoxification effects (Xie et al., 2012). Hard protective shell of Onchidiacea mollusc species secreted viscous fluid that could prevent it from predation. The lipid soluble extract, Onchidal™ was found to be the major product of *Onchidella binneyi* that could inhibit the activity of acetylcholinesterase enzyme in an irreversible pattern (Moodie et al., 2019). Turbotoxin A from *Turbo marmorata* (gastropod) was active against acetylcholinesterase enzyme (IC_{50} 28 mM), and the compound was not found to interfere with the peripheral nervous system (Moodie et al., 2019). Acetylcholinesterase inhibition activity was previously reported for the oyster, *Crassostrea virginica* (Bolton-Warberg, Coen, & Weinstein, 2007). The clam, *M. meretrix* displayed hypolipidemic pluralities (Wei et al., 2007). Potent antihypercholesterolemic (IC_{90} 1.21 mg/mL) property of *A. marginatus* attributed its utilities as natural sources of bioactives in food supplements and nutraceuticals (Krishnan & Chakraborty, 2019).

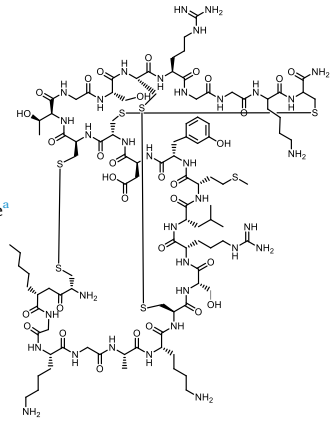
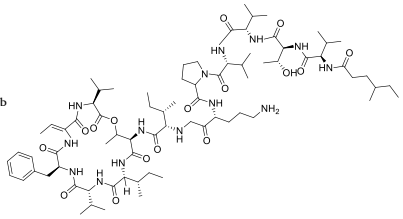
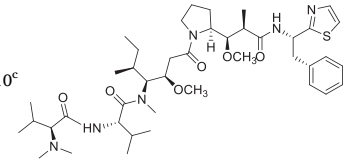
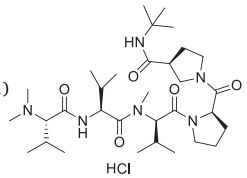
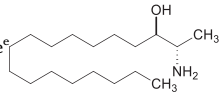
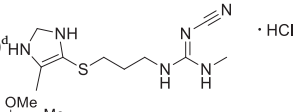
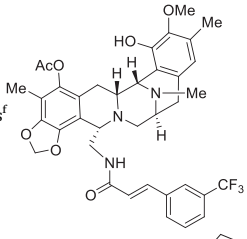
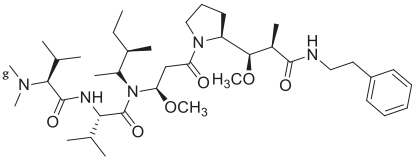
9. Molluscan pharmaceuticals: A modern pipeline perspective

Natural products from the marine and estuarine molluscs were regarded as the backbone of modern therapeutics and pharmaceuticals. Recently, wide-range of bioactive natural products isolated from the molluscs were used in the formulation of pharmaceutical drugs (Table 6; Fig. 5) (Simmons et al., 2005). The mollusc-derived drug, ziconotide was approved by the Food and Drug Administration (FDA) (Mayer et al., 2010). Cytarabine and vidarabine were the first two marine natural products, which were added into the "pharmacopoeia" in 1974, for treating the human diseases. Following that, it has been taken through 30 years, for the identification and approval of the mollusc-derived ziconotide, and it was added to the "pharmacopeia" in 2004 (Mayer et al., 2010; Prommer, 2006). Dolastatin-10 and its synthetic analogs from *D. auriculata* were under phase-II clinical trials as anticancer agents (Madden et al., 2000). Kahalalide F identified from *Elysia rufescens* (Lopez-Macia et al., 2001), and ES-285 from bivalve, *Mactromeris polynyma* completed the phase-I clinical trials (Den Brock et al., 2005; Faircloth & Cuevas, 2006). Some important pharmaceuticals of molluscan origin with various therapeutic potentials were described below.

9.1. Ziconotide (Prialt)

A synthetic equivalent of 25-amino acid peptide, ω-conotoxin MVIIA was initially isolated from the venom of *Conus magus* (Bingham, Mitsunaga, & Bergeron, 2010). It is an effective analgesic with novel mechanism of action (Bingham et al., 2010). Different subtypes of voltage-gated calcium channels were identified in the nervous system. Ziconotide could reversibly block the *N*-type calcium channels situated on the primary nociceptive afferent nerves in superficial layers of dorsal horn of the spinal cord. Binding of ziconotide to the presynaptic *N*-type calcium channels could reduce the generation of excitatory neurotransmitters from the primary afferent nerves (McGivern, 2006). In opiate-based therapies, the tolerance levels to drugs were found to be the major limiting factor, whereas ziconotide did not produce any tolerance levels (McGivern, 2006). Detailed experiments found the inability of ziconotide to cross the blood–brain-barrier, and could be delivered into the spinal theca using implantable pump or temporarily by external microinfusion device (McGivern, 2006). It was accredited by the FDA in December 2004, and presently labeled for management of chronic pain in patients with AIDS or cancer (Rauck, Wallace,

Table 6
Current pipeline of pharmaceuticals from molluscs.

Clinical status	Compound name and structure	Studied mollusc	Trademark	Compound class	Institution/Company	Disease area
Approved by FDA	Ziconotide[a] 	*Conus magus* (snail)	Prialt	Peptide	Elan Corporation	AIDS or cancer
Phase-II trials	Elisidepsin[b] 	*Elysia rufescens* (slug)	Irvalec	Depsipeptide	Pharmamar company	Cancer
Phase-II trials	Dolastatin 10[c] 	*Dolabella auricularia* (sea hare)	NA	Peptide	Celltrion pharmaceutical company	Cancer
Phase-II trials	Tasidotin-HCl[d] (ILX-651) 	*Dolabella auricularia*	NA	Depsipeptide (dolastatin-15 analog)	NA	Cancer
Phase-I trials	Spisulosine[e] 	*Spisula polynyma* (surf clam)	NA	Amino alcohol	Pharmamar Group	Cancer
Phase-I trials	Cematodin-HCl (LU-103793)[d] 	*Dolabella auricularia*	NA	Pentapeptide (dolastatin-15 analog)	NA	Cancer
Phase-I trials	Zalypsis[f] 	*Jorunna funebris* (slug)	Zalypsis	Alkaloid	Pharmamar company	Cancer
Phase-I trials	TZT-1027 [g] 	*Dolabella auricularia*	NA	Peptide (dolastatin-10 analog)	NA	Antivascular

[a] Rauck, Wallace, Burton, Kapural, & North, 2009; Williams, Day, & Heavner, 2008; [b]Mayer et al., 2010; [c]Poncet, 1999; [d]Kang, Choi, Seo, & Park, 2018; [e]Cuadros et al., 2000; [f]Scott & Williams, 2002; [g]Riely et al., 2007.

Burton, Kapural, & North, 2009). Prialt® was commercialized by Elan Corporation, PLC (retrieved from http://www.elan.com/therapies/products/prialt.asp), and ziconotide was approved to market in the Europe, Middle East and Africa (Williams, Day, & Heavner, 2008).

9.2. Elisidepsin (Irvalec, PM02734)

It is cyclic a depsipeptide belonging to dehydroaminobutyric acid containing peptide family of compounds, called as kahalalides, which were isolated from the herbivorous mollusc, *E. rufescens* (Lopez-Macia et al., 2001). This pharmacophore agent successfully completed phase-II clinical trials with antitumor activities in the wide variety of cancer cells, including lung, breast, pancreas, colon, and prostate. Its primary mechanism of action is yet to be elucidated, even though it was reported that this compound could induce oncolytic rather than apoptotic cell death. It was reported to inhibit the expression of certain genes involved in the DNA replication, proliferation of tumor cells and their growth (Mayer et al., 2010). Elisidepsin™ is being developed by Pharmamar (PM02734) (http://www.pharmamar.com/products.aspx).

9.3. Zalypsis (PM00104)

It is a DNA-binding alkaloid, which was similar to jorumycin, and was isolated from the mucus and skin of the Pacific nudibranch mollusc, *Joruna funebris* (Scott & Williams, 2002). It was found to bind the guanine in the selected DNA triplets, and thereafter the DNA adducts gradually could give rise to the double-strand breaks, S-phase arrest, and finally apoptosis in the cancer cells. Preclinical studies described its potent antitumor activities in the prostate, renal, breast and colon cancer (http://www.pharmamar.com/products.aspx), and the alkaloid is currently under its phase-II clinical trials.

9.4. Dolastatins

These were cyclic or linear peptides identified from the marine mollusc, *D. auricularia*. Among the dolastatins, dolastatin-10 and 15 displayed promising antiproliferative action (Poncet, 1999). Dolastatin-10 was the most potent antiproliferative dolastatin, and was found as a linear pentapeptide with several significant amino acid residues. Dolastatin-10 was selected for the clinical trials owing to the favorable preclinical advantages, and was under phase-II clinical trials as anticancer drug (Poncet, 1999). Its mode of action involves the inhibition of microtubule assembly, and tubulin polymerization followed by the cells arrest in the metaphase (Pathak, Multani, Ozen, Richardson, & Newman, 1998). Lesser synthetic yield and water solubility along with the structural complexity of dolastatins were the barriers for their wider clinical evaluations (Poncet, 1999). Synthetically, various analogs of dolastatin-10 were prepared, and among those the drug named as TZT-1027 with antivascular activity was identified. TZT-1027 was found to possess *in vivo* antiangiogenic activity in the chorioallantoic membrane embryo, and human umbilical vein endothelial cells. However, it did not exhibit anticancer activity in phase-II clinical trials (Riely et al., 2007). Dolastatin-15 obtained from *D. auricularia* was not clinically investigated, but its water-soluble derivatives named as LU-103793 (cematodin) and ILX651 (tasidotin) were formulated as anticancer drugs for the clinical studies (Kang et al., 2018). In this, LU-103793 could complete the phase-I clinical trial for curing of cancer, but the phase-II trial was interrupted. ILX-651 could complete the phase-I clinical trial, and the phase-II trial was suggested due to no cardiotoxicities. Tasidotin™ has completed the phase-II trials against breast, prostate cancers and melanoma (Kang et al., 2018).

9.5. Keenamide-A

It is a cyclic hexapeptide isolated from the mollusc *Pleurobranchus forskalii*, and exhibited antitumor activities against the cancer cell lines, like MEL-20, A-549, P-388, and HT29 through unidentified mechanisms (Wesson & Hamann, 1996).

9.6. Kulokekahilide-2

The cyclic depsipeptide, kulokekahilide-2 was a potent aurilide-type of compound, which was firstly isolated from *Philinopsis speciosa*. Structural similarities with aurilides confirmed that it was biosynthesized by the marine cyanobacteria, and it exhibited anticancer activities against various cell lines, such as P388, SKOV-3, MDA-MB-435 and A-10 (Nakao et al., 2004).

9.7. Spisulosine ES-285

The compound was found to be a potent antiproliferative alkyl amino alcoholic compound, and was identified from *Spisula polynyma* by the Spanish Pharmamar group. Spisulosine exhibited an intriguing mechanism of action, and the molecular target of this molluscan alkyl group was found to be Rho (GTP-bp). The compound was undergoing phase-I clinical trials as an antiproliferative agent (Cuadros et al., 2000) ().

10. Publications in the subject of high value compounds from molluscs: The trends from the past

The annual reviews of marine natural products (MNPs), inclusive of the phylum Mollusca were initiated by late Professor D. John Faulkner in 1984, and was continued by the New Zealand group from 2003 till 2019. These reviews included the structures of new secondary metabolites and their revisions. The increased numbers of publications with respect to the marine molluscan natural products described the significance of the organisms. The natural product reports on “marine natural products” of molluscan origin described more than 604 publications between 1984 and 2002 (Faulkner, 1984; 1986; 1987; 1988; 1990; 1991; 1992; 1993; 1994; 1995; 1997; 1998; 2000; 2002), and more than 683 publications between the period spanning between 2003 and 2019 (Blunt et al., 2003, 2004, 2005, 2006; 2007; 2008; 2009; 2010; 2011; 2012; 2013; 2015; 2016; 2017; 2018; Carroll et al., 2019) (Fig. 6). Benkendorff (Benkendorff, 2010) described 146, 11, and 878 published reports on the pharmaceutical effects of bivalves, cephalopods, and gastropods, respectively. The database of marine natural product literature, MarinLit described a total of 2456 publications by using the keywords “molluscs or molluscan” (MarinLit, accessed on 01/10/2019). A recent search in Sci-Finder, using the keywords “bivalves” retrieved 12,594 publications, whereas the keyword “cephalopods” sorted out 1724 publications, and that of “gastropods” fetched 4941 publications (Sci-Finder, accessed on 15/09/2019). Search in PubMed using the molluscan derived drugs, such as “ω-conotoxin MVIIA, SNX-111, ziconotide or prialt” retrieved 60,521 publications in the peer-reviewed literatures (PubMed, accessed on 20/09/2019). Similarly, another drug “elisidepsin or kahalalides” search in PubMed sorted out a total of 35 publications (PubMed, accessed on 21/09/2019). The keywords, “zalypsis or jorumycin” were described by 34 publications, and the search terms like, “dolastatins, dolastatin 10, dolastatin 15, LU-103793, cematodin, ILX651 or synthadotin” described 15 publications in the PubMed (PubMed, accessed on 22/09/2019). The keyword “keenamide A” retrieved 2 publications, whereas the “kulokekahilide-2 or aurilide” retrieved 11 publications, and “spisulosine ES-285” was reported by a total number of 32 publications in the PubMed search (PubMed, accessed on 24/09/2019). A recent search was carried out on the pharmacological activities, such as “antioxidant, anti-inflammatory, antihypertensive, antidiabetic, antimicrobial, antiviral and anticancer” effects of some selected molluscan species (*H. diversicolor*, *H. discus*, *B. spirata*, *B. zeylanica*, *B. spinosa*, *C. ramosus*, *P. malabarica*, *V. cyprinoides*, *M. meretrix*, *P. viridis*, *P. canaliculus*, *C. madrasensis*, *L. duvauceli*, *C. indicus*, *S. pharaonis*, *S. inermis*, *A. marginatus*) in the Google Scholar

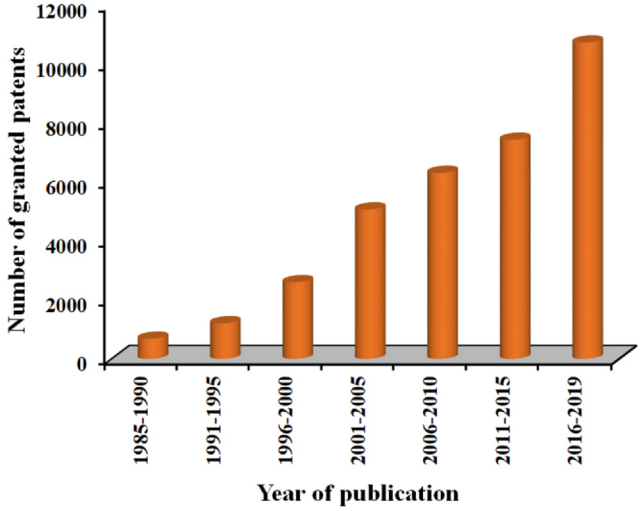


Fig. 14. Comparison of granted patents from 1985 to 2019 in the area of molluscan research (retrived from Google patents, accessed on 12/10/2019).

(accessed on 13/10/2019). It was described that, around 23% of publications were related to the pharmacological activities of *H. discus* followed by those associated with *P. viridis* (20%), *M. meretrix* (15%) and *H. diversicolor* (12%), in descending order. The emerging trendin the number of publications in the field of molluscan research, particularly in the pharmacological effects of molluscs attracted the attention of marine natural product chemists and medical researchers to focus on this diverse phylum.

11. Emerging trends in patents from the marine and estuarine molluscs

The number of granted patents in the field of molluscan research were found to increase in the recent years. Comparative study of the granted patents in this area from 1985 to 2019 were carried out, which includes the cultivation, harvesting, preservation of molluscs, along with their therapeutic and nutraceutical utilities (retrived from the Google patents as on 12/10/2019) (Fig. 14). The number of granted patents were found to be 2% in between the years of 1985 to 1990, and which was increased to more than 30% during 2016–2019. Herein, we have only reviewed the patents related to the pharmaceutical and nutraceutical applications of the molluscs (Table 7). The powder of abalone shell was incorporated into a patented formula for treating burns without pain and scaring (Lee, 1993). Lyprinol®, the lipid extract of *P. canaliculus* was patented for arthritis and asthma with proven range of clinical trials (Gibson, 2000; Halpern, 2000). Lyprinol® was found to be effective in the prevention of inflammatory bowel disease (Tenikoff, Murphy, Le, Howe, & Howarth, 2005), and the therapeutics including the extracts of *P. canaliculus* were patented for use in the treatment of side effects of analgesics caused in the gastro-intestinal tracts (McFarlane & Croft, 1984). Commercialized nutraceutical supplement, Cadalmin™ Green Mussel extract (Cadalmin™ GMe) containing 100% natural marine bioactive anti-inflammatory ingredients extracted from the Asian green mussel *P. viridis* for use against rhumatoid arthritis pain was patented (Chakraborty et al., 2010a, 2010b). Active principles in Cadalmin™ GMe displayed potential capacities to attenuate experimentally induced inflammation, and can act as dual inhibitors of 5-lipoxygenase and cyclooxygenase-2 pathways, thereby down-regulating the biosynthesis of inflammatory leukotrienes and prostaglandins. Mean lethal dose (LD_{50}) of the product was greater than 4000 mg/kg body weight of the animal subjects that indicated the safety of the product (Chakraborty, Joseph, & Chakkalakal, 2014b). Cosmetic cream made from the mineral or organic phases of mother of pearl, *Pinctada maxima* was patented for its dermatological functions (skin regeneration process) and wound healing properties (Camprasse & Camprasse, 1998). The patent document, WO2006122296 described the identification of four novel cerebroside compounds, named as turbostatin 1–4 from the marine mollusc, *Turbo stenogyrus*. These compounds exhibited significant inhibition against the growth of murine and human cancer cells, and were found to be useful against various neoplastic ailments (Pettit & Tang, 2006).

Bivalve mussels belonging to the class of Mytillidae were recently subjected to several patents as prospective sources of antimicrobial (De Faire, 1999) and antiviral (Bichurina et al., 1994; Rothman, 1984) peptides. An anti-HIV formulation with application number 60/280,086, from the Indian green mussel, *P. viridis* was patented (Patent Number US6770302B2/en) (Mitra & Chatterji, 2002). The anticancer agent, kahalalide F isolated from *E. rufescens* was patented for anticancer activities against colon, breast, ovarian, and lung cancer, and particularly against androgen-independent prostate cancer (Patent Number US 2004067895A1) (Faircloth, Nuyen, & Weitman, 2004; Lopez-Macia et al., 2001; Faircloth and Cuevas, 2006). The compound was also active against the pathogenic microorganisms, such as HIV or AIDS, and was currently undergoing phase-II clinical trials in Europe (Albericio et al., 2008). Acid hydrolyzates of *M. edulis* and *M. galloprovincialis* were patented for the use as a prophylactic, antipyretic, and as a therapeutic radiopharmaceutical medication (Kudrjasov, Perov, Gontsarenko, Deev, Lebedeva, & Casovskoy, 1994). Methods of cancer treatments using the bivalve, *P. canaliculus* was patented (application number 60/454,340). Production of protein hydrolysate from the zebra mussel as food products, medical-prophylactics, and its use in medical, microbiology, and veterinary organizations were patented (Vladimirovna & Ien, 2009). Pharmaceutical composition of the mussel hydrolysate of *P. viridis* was formulated and patented for the inhibition of osteoclast formation, and these compositions were found to be non-toxic to other cells (Wani, Parab, & Chatterji, 2005). Trachyostracous mussel extract was patented for the use in the preparations of anti-SARS (anti-severe acute respiratory syndrome), anti-influenza, and immunomodulatory drugs (Chinese patent, 2009). An antioxidative composition of the peptide isolated from the protein hydrolysate of *M. coruscus* as an active ingredient to prevent the process of ageing was patented (Korean patent number KR20120049042A, 2012).

12. Biotoxins from molluscs: Potential candidates for the development of pharmacophores

Majority of the molluscan species were reported to significantly contribute towards the benefits of human health and nutrition, along with economic developments due to their commercial importance. Even though, the human intoxication was reported by the consumption of molluscs due to the production of biotoxins as part of their defence mechanisms. Chemically, the biotoxins were classified as azaspiracid, brevetoxin, okadaic acid, pectenotoxin, saxitoxin, cyclic imine, and yessotoxin. These biotoxins attracted the attention of researchers owing to their potent biological activities, and as candidates for drug developments as well as biological probes for physiological analyses (Uemura et al., 1995). Important shellfish poisoning were classified as amnesic shellfish poisoning (ASP), diarrhetic shellfish poisoning (DSP), neurotoxic shellfish poisoning (NSP), and paralytic shellfish poisoning (PSP) (Table 8). Cyclic polyether derivatives, such as brevetoxins could pass through the cell membranes, and interact with neurotransmitter receptors resulting in neurotoxicity and various neurological disorders (Ishida et al., 2004). Brevetoxin B5 was reported from *Austrovenus stutchburyi* (cockle), *C. gigas* and *P. canaliculus* (Murata, Satake, Naoki, Kaspar, & Yasumoto, 1998), whereas brevetoxin B2 was isolated from *P. canaliculus* (Ciminiello et al., 2007a). Okadaic acid and dinophysistoxins were found to inhibit the protein phosphatases, and resulted in diarrheagenicity and neurotoxicity. Oxazinin and its derivatives were reported from *M. galloprovincialis* (Ciminiello et al., 2007), and were found to be responsible for DSP poisoning (Ciminiello et al., 2006).

Table 7
Examples of patents in the area of pharmaceuticals or nutraceuticals reported from the molluscan species

Studied mollusc	Patent number	Description of the invention	References
Pinctada maxima	US5773034	Cutaneous rejuvenating, healing, dermatological purposes, skin problems	Camprasse & Camprasse, 1998
Perna canaliculus	US4455298	Pharmaceutical preparations with gastroprotective action, antiulcer potentials	McFarlane & Croft, 1984
Perna viridis	IP302803	The process to concentrate anti-inflammatory principles	Chakraborty et al., 2010a
Perna viridis	IP303813	Anti-inflammatory product against pro-inflammatory enzymes	Chakraborty et al., 2010b
Turbo stenogyrus	WO2006122296	Isolation and structure of turbostatins 1–4, inhibition activity against cancer cell growth, inhibition of several murine and human cancer cell lines, useful in the treatment of various neoplastic diseases	Pettit & Tang, 2006
Elysia rufescens	US20040067895A1	Kahalalide F formulation, potent against *in vitro* human lung carcinoma A-49 and human colon carcinoma HT-29	Faircloth, Nuyen, & Weitman, 2004
Elysia rufescens	PL356800A1	Kahalalide compounds, potent against pathogenic microorganisms, which cause the opportunistic infection of HIV/AIDS	Albericio et al., 2004
Mytilus edulis *Mytilus galloprovincialis*	DE4309339A1	Biologically active pharmaceutical product, prophylactic and therapeutic radiopharmaceutical functions in human and animal, anti-inflammatory effects, blood production, stimulates regeneration processes after injuries and operations, effective against psychological or physical stress	Kudrjasov et al., 1994
Perna viridis	US6905710B2	Pharmaceutical composition useful for inhibition of osteoclast formation, inhibition of osteoclast formation	Vladimirovna & Ien, 2009
Perna canaliculus *Mytilus edulis*	WO2006128244A1	Enzyme-assisted production of mussel oils, which exhibited significant inhibition of mammalian cyclooxygenases 1 and 2, anti-inflammatoryactivity	Macrides & Broadbent, 2006
Telescopium telescopium	291906	Bioactive compounds, potential anticancer or antiproliferative agent	Roy & Datta, 2009
Mytilus galloprovincialis	WO2001004294A1	Peptides derived from molluscs, antimicrobial activity	Roch, Mitta, Hubert, & Noel, 2001
Abalone	EP2280726A1	Nutraceutical, used in prophylaxis of viral infection in mammal, antiviral agent	Cuthbertson, 2011

Saxitoxins were reported from *Saxidomus giganteus* (Wiese, D'Agostino, Mihali, Moffitt, & Neilan, 2010), *Mytilus chilensis* and *Tagelus dombeii*, and were found to be responsible for paralytic poisoning (Terrazas, Contreras, & Garcia, 2017). The molluscs, such as *M. edulis*, *Siliqua patula*, *Mya arenaria* and *P. magellanicus* were reported for the production of domic acid, which could cause ASP poisoning (Farabegoli, Blanco, Rodríguez, Vieites, & Cabado, 2018). Another bivalve, *P. muricata* was reported for its acute toxicity in mice due to the production of pinnatoxins, such as pinnamine and pinnaic acid (Takada, Iwatsuki, Suenaga, & Uemura, 2000). The known spiroimine toxins, namely pinnatoxin A/D and pinnatoxin E-G were isolated from the digestive glands of *C. gigas* (Selwood et al., 2010). Pinnatoxins and their fatty acid ester metabolites were identified from the mussel *M. edulis* (McCarron, Rourke, William, Pooley, & Quilliam, 2012). Pectenotoxin-4 and 7 were purified from the Japanese scallop, *P. yessoensis* (Sasaki, Wright, & Yasumoto, 1998). Even though there were occurrences of mollusc biotoxins, these compounds were of interest for marine natural product chemists to develop several life-saving drugs.

13. Molluscs: Future aspects and conclusion

Till date, only a small proportion of the molluscan species was used towards the isolation and characterization of novel bioactive secondary metabolites. The knowledge of existing ethnopharmacological utilities of molluscs could lead to greater developments and formulations in healthcare as well as therapeutic interest. Preliminary data with regard to the bioactive potential of bivalves, cephalopods and gastropods appropriately suggested their importance as health food, when compared to other classes of phylum mollusca. Commercial significance of the molluscs recognized these as valuable fishery resources in various parts of coastal regions of the world. The nutritive and health benefits of the molluscs suggested that these could be added to our daily diets to improve health benefits and enhancement of immune systems. This review revealed that the marine and estuarine molluscs could be utilized as valuable bioresources to develop new therapeutic and high-value constituents with wide-range of pharmacological activities. Notably, the percentage of granted patents from 2016 to 2019 in the area of molluscan research was increased to more than 30%, which recognized the significance of the molluscan phylum to develop high value compounds of pharmaceutical significance. More than 1334 secondary metabolites with potent bioactive properties were isolated and characterized from the marine molluscs between the periods of 1984 to 2019. In particular, the studies on scaphopoda and polyplacophora class of molluscs would be regarded as valuable for further studies owing to their availability and reasonably larger size, along with the knowledge of their traditional uses. Due to the promising pharmacological profiles of the molluscs, further studies are warranted to develop medications and nutraceutical products to alleviate several life-threatening ailments. The bioactive compounds from the molluscs of marine and estuarine origin could also be utilized in the development of potential therapeutic templates and functional food products.

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Compliance with Ethical Standards

Human Rights Statement

This article does not contain any studies with human participants performed by any of the authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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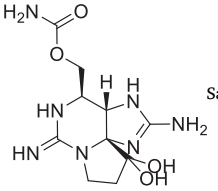
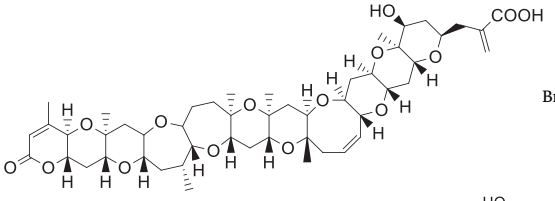
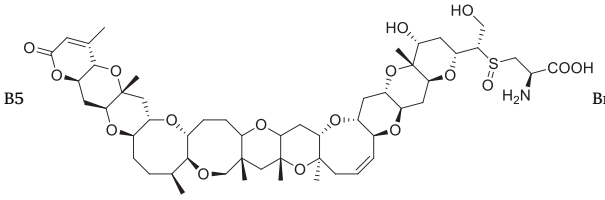
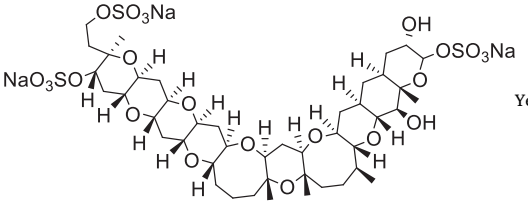
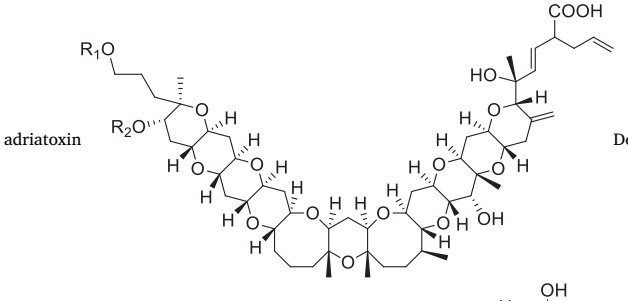
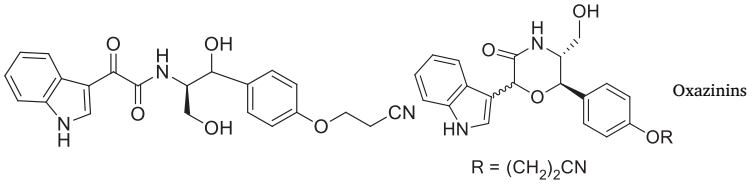
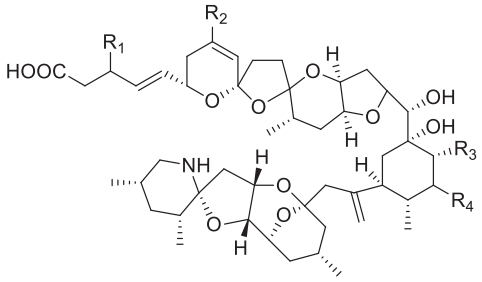
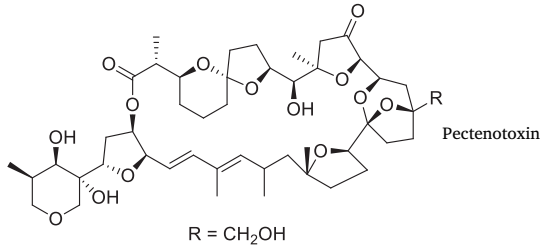
Table 8
Classification of molluscan biotoxins and their side effects in humans

Molluscan biotoxins	Source	Symptomatology
Paralytic shellfish poisoning (PSP)		
 Saxitoxin	*Alexandrium* spp., *Pyrodinium bahamense*	Gastrointestinal and/ or paralytic problems, recovery or death
Neurotoxic shellfish poisoning (NSP)		
 Brevetoxin	*Karenia brevis*	Gastrointestinal, neurological, and respiratory problems
 B5 Brevetoxin B2		
Diarrhetic shellfish poisoning (DSP)		
 Yessotoxinanalogue,	*Protoceratium reticulatum, Gonyaulax spinifera*	Lack of observations in humans
 adriatoxin Desulfoyessotoxin		
 Oxazinins	–	Gastric problems
Miscellaneous		

(*continued on next page*)

Table 8 (*continued*)

Molluscan biotoxins	Source	Symptomatology
 Azaspiracid **278** R_1 = OH, R_2 = R_4 = H, R_3 = Me **279** R_1 = R_2 = H, R_3 = Me, R_4 = OH **280** R_1 = OH, R_2 = Me, R_3 = R_4 = H **281** R_1 = R_3 = H, R_2 = Me, R_4 = OH **282** R_1 = OH, R_2 = R_3 = Me, R_4 = H	*Amphidoma languida, Azadinium spinosum*	Gastrointestinal symptoms
 Pectenotoxin R = CH_2OH R = COOH	Dinophysis spp.	Gastrointestinal problems

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodres.2020.109637.

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