Structural Diversity of Secondary Metabolites from Marine-Derived Bacillus

Subjects: Psychology, Biological

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The marine is a highly complex ecosystem including various microorganisms. Bacillus species is a predominant microbialflora widely distributed in marine ecosystems. *Bacillus* species can grow rapidly and tolerate extremely adverse environmental conditions such as extreme ambient temperature, salinity and pH, high pressure and nutrient deficiency. *B. subtilis* can adopt several responses when faced with the depletion of essential nutrients, including motility, secretion of extracellular enzymes, genetic transformation, antibiotic production, and finally sporulation. The genus *Bacillus* is a prolific producer of bioactive metabolites, including more than 350 kinds of rod-shaped and Gram-positive bacteria.

Keywords: marine microorganism ; Bacillus ; structural diversity

1. Introduction

The ocean is a highly complex ecosystem, a rich and underdeveloped treasure house containing a wide variety of biological resources including aquatic species and various microorganisms [1][2][3]. Natural products, especially small molecules isolated from biological sources, have long been regarded for their huge potential in human medicine and are still gaining traction [4]. Marine microorganisms produce many undiscovered molecules with unprecedented structures and pharmacological activities in an extreme living environment [2]. Therefore, it is commonly recognized that marine microbes constitute a promising source of novel metabolites with considerable therapeutically potential for new drug screening and development [3][5][6][7][8].

Bacillus species is a predominant microbialflora widely distributed in marine ecosystems [9][10]. *Bacillus* species can grow rapidly and tolerate extremely adverse environmental conditions such as extreme ambient temperature, salinity and pH, high pressure and nutrient deficiency [11]. *B. subtilis* can adopt several responses when faced with the depletion of essential nutrients, including motility, secretion of extracellular enzymes, genetic transformation, antibiotic production, and finally sporulation [12]. The genus *Bacillus* is a prolific producer of bioactive metabolites, including more than 350 kinds of rod-shaped and Gram-positive bacteria [13]. Thereinto, *B. subtilis*, *B. licheniformis* and *B. amyloliquefaciens* possess potential value as therapeutic agent candidates on account of their ability to produce bioactive secondary metabolites [14][15][16][17].

In recent years, a variety of secondary metabolites of marine *Bacillus* species have been studied, including lipopeptides [18], polyketides [19], non-ribosomal peptides [20], macrolides [16][21], and glycopeptides [9]. Several natural products were isolated from the marine organisms for drug development by traditional means of bioactivity-guided methods and chemical structure elucidation. More precise analytical methods, such as LC-MS and NMR spectroscopy guided metabolic profiling and dereplication of a crude extract, also promoted the emergence of new secondary metabolites [22][23][24]. Some novel technologies, such as improved genome mining methods, have propelled natural products in the field of drug discovery [25]. The marine hosts a huge variety of organisms adapted to the specific environment, which should result in the production of a wide range of unique biomolecules [7]. The production of secondary metabolites is normally associated with the bacterium's response to a growth-limiting environment; hence, exploring the high diversity of marine environments may uncover multiple compounds with unique structures and biological activities [26]. For example, most of this industrial *Bacillus pumilus* group (*Bp* group) have been isolated from terrestrial ecosystems at present. By contrast, members of the *Bp* group are ubiquitous and diverse in marine environments, but less explored [27].

According to studies, these compounds have a wide range of biological activities, viz., antimicrobial [28][29], anticancer [30][31][32], antivirus [33], antifungal, promotion of plant growth [34], immunosuppressive, antituberculosis, antimycoplasmic and exceptional surfactant [35], indicating their promising medicinal, agricultural and industrial potential. Over the past decades, *Firmicutes phylum* were found to be the marine-derived bacteria producers of the most antimicrobial activity, *Bacillus* strains specifically [26]. Sequel of genomic analyses demonstrated the prospect of marine *Bacillus* species

producing wide-ranging polyketide classes of antibiotic agents, such as macrocyclic lactones, bacillaene, macrolactins, and difficidins [36][37]. Polyketide, as conspicuous bactericidal agents in the human health area, was reported to produce by multifunctional microbial polyketide synthase (pks) complex [38]. Difficidins are a polyketide class of polyenes, which were reported to biosynthesize by type I *pks* encrypted in the *dif* operon and were recognized to hinder bacterial pathogens [35]. Moreover, polyketides are the most structurally diverse and pharmacologically relevant natural products with low toxicity and high efficacy, many of which exhibit cytotoxic effects on cancer cells.

2. Cyclic Lipopeptides

Cyclic lipopeptides (CLPs) are common secondary metabolites isolated from marine-derived *Bacillus*. The CLPs are a class of metabolites with structural diversity produced by multifarious bacterial genera [39]. There are three families of CLPs being of particular importance, namely surfactins, iturins and plipastatins, all consisting of a short cyclic oligopeptide linked to the tail of a fatty acid [14]. Surfactin sequences comprise of seven amino acids and a *β*-hydroxy fatty acid chain containing 12–16 carbons [40]. The iturin family sequences are composed of heptapeptides and a *β*-amino fatty acid chain of 14–17 carbon atoms, which consists of bacillomycin D, F, L, Lc, iturin A, A_L, C and mycosubtilin (**Figure 1**) [41]. The plipastatin family comprise of ten amino acids and a *β*-hydroxy fatty acid containing 14–18 carbon atoms [42]. **Figure 2** lists the structures of cyclic lipopeptides produced by marine-derived *Bacillus* species.

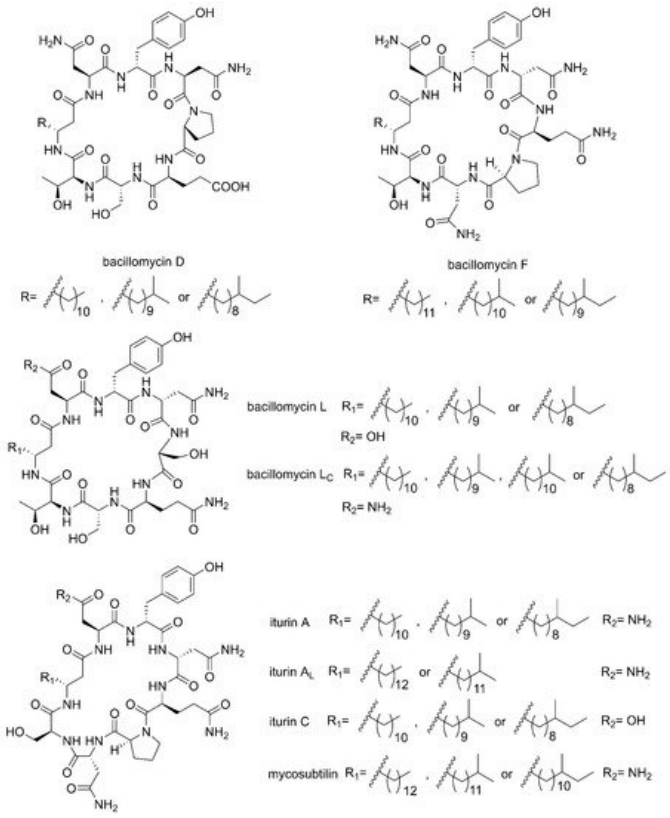

Figure 1. The structures of iturin family members (bacillomycin D, F, L, Lc, iturin A, AL, C and mycosubtilin).

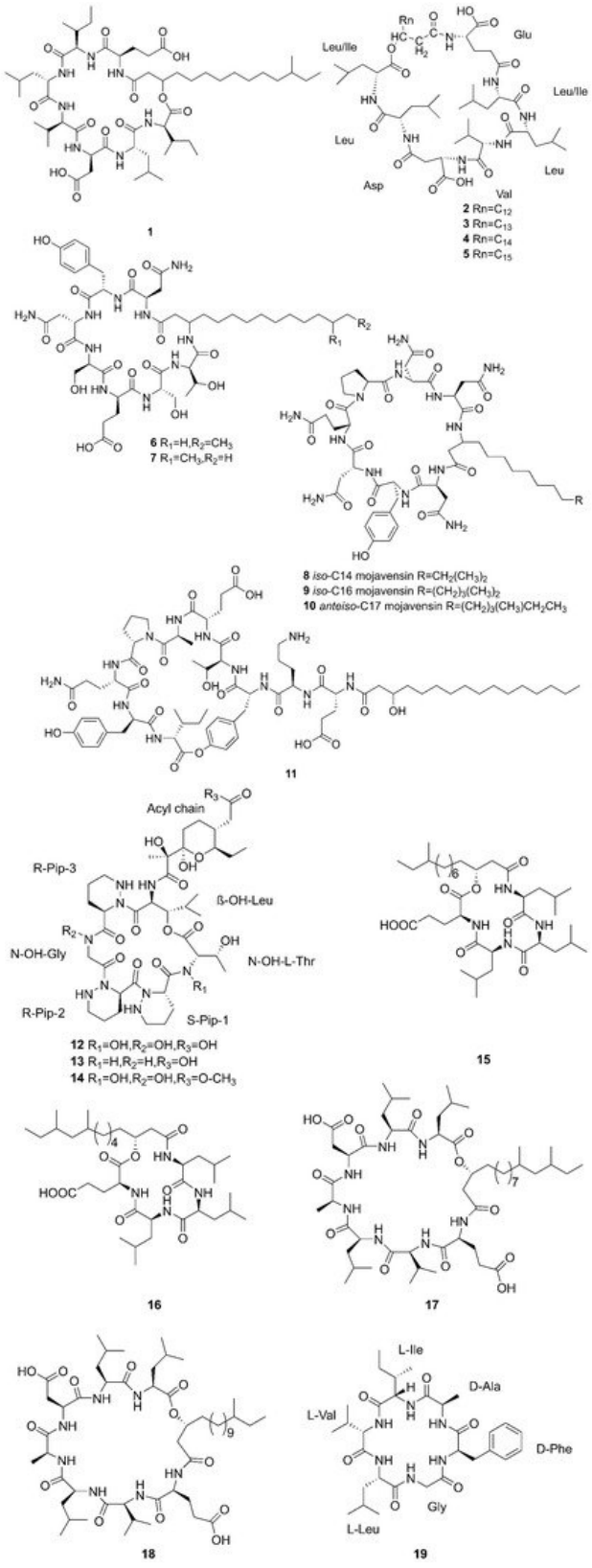

Figure 2. Cyclic lipopeptides produced by marine-derived *Bacillus* species.

Compounds **1–5** belong to surfactin family. A new CLP surfactin named *anteiso*-C_{15} $Ile_{2,7}$ surfactin (**1**) was isolated from *B*. *velezensis* SH-B74 in the China Center for Type Culture Collection (CCTCC), which collected from the marine sediments, comprising of an *anteiso*-C_{15} type saturated fatty acid chain, and a peptidic backbone of L-Glu_1, L-Ile_2, D-Leu_3, L-Val_4, L-Asp_5, D-Leu_6, L-Ile_7 [43]. Rn-Glu^1-Leu/Ile^2-Leu^3-Val^4-Asp^5-Leu^6-Leu/Ile^7 (**2–5**) belonging to surfactin homolog were isolated from *B*. *licheniformis* MB01 collected from sediments in the Bohai Sea, China [44]. Compounds **6–10** belong to the iturin family. A novel lipopeptide antibiotic bacillopeptin named bacillopeptin B_1 (**6**) and a known compound, bacillopeptin B (**7**) were detected in the fermentation broth of a marine sediment-derived *B. amyloliquefaciens* SH-B74 collected from sediments in the South China Sea. More precisely, compound **6** as a member of bacillopeptin family has the same amino-acid sequence and the same molecular weight as compound **7**, but has a different fatty-acid residue [22]. Compounds **8–10** were characterized as cyclic lipopeptides with saturated *β*-amino fatty acid chain residues, *iso*-C14 mojavensin, *iso*-C16 mojavensin, and *anteiso*-C17 mojavensin, all of which were produced by a marine-derived *B.*

mojavensis B0621A obtained from the mantle of a pearl oyster *Pinctada martensii* in the South China Sea [45]. In addition, plipastatin A1 (**11**), belonging to the plipastatin family, was obtained by solidphase extraction and reversed-phase high-performance liquid chromatograph (RP-HPLC) from the fermentation broth of a marine sediment-derived *B. amyloliquefaciens* SH-B74 in the CCTCC [46]. A new cyclic hexapeptide with three piperazic acids (N-OH-Thr, N-OH-Gly, *β*-OH-Leu) named dentigerumycin E (**12**) and two reported derivatives, 2-N, 16-N-deoxydenteigerumycin E (**13**) and dentigerumycin E methyl ester (**14**), were isolated from coculture of marine *Streptomyces* and *Bacillus* strains collected together from the intertidal mudflat in Wando, Republic of Korea. It is worth mentioning that only compound **12** showed antiproliferative and antimetastatic activities against human cancer cells, suggesting that 2-N-OH, 16-N-OH, and 37-OH (carboxylic acid) are essential for the activities [25]. Two novel cyclic lipopeptides, bacilotetrin A (**15**) and bacilotetrin B (**16**), possessing three leucines and one glutamic residue cyclized with a lipophilic 3-hydroxyl fatty acid, were isolated from *B. subtilis* 109GGC020 in the sediments from the Gageocho of southern reef, Republic of Korea [12]. Additionally, gageopeptins A (**17**) and B (**18**), two novel cyclic lipopeptides, were isolated from the same strain in the same sediments as above [47]. A new cyclic hexapeptide named bacicyclin (**19**) was purified from *Bacillus* sp. BC028 associated with the blue mussel *Mytilus edulis* collected from the western shore of the Baltic Sea in Germany [48].

3. Diketopiperazines

Cyclicpeptide diketopiperazines consist of residues of two amino acids and mevalonic acid [49]. **Figure 3** lists the structures of diketopiperazines that were produced by marine-derived *Bacillus* species.

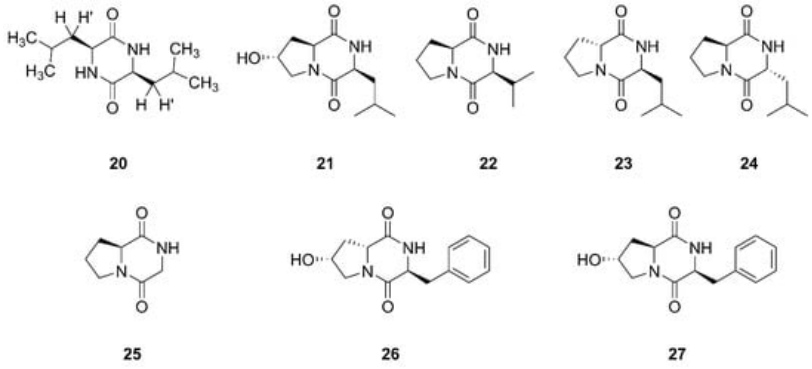

Figure 3. Diketopiperazines produced by marine-derived *Bacillus* species.

Compound **20** was established as a diketopiperazine (3S, 6S)-3,6-diisobutylpiperazine-2,5-dione, which was isolated from the ethyl acetate extract of the culture broth of *Bacillus* sp. SPB7. This strain SPB7 was obtained from marine sponge *Spongia officinalis* collected from the Palk Bay of Bengal, India. In particular, this is the first time that compound **20** had been isolated from a sponge-associated microbe [50]. Finally, seven cyclic dipeptides compounds **21**–**27** were identified and characterized as cyclo (L-leu-trans-8-hydroxy-L-pro), cyclo (L-val-L-pro), cyclo (D-pro-L-leu), cyclo (L-pro-D-leu), cyclo (gly-L-pro), cyclo (L-phe-cis-8-hydroxy-D-pro), and cyclo (L-phe-trans-8-hydroxy-L-pro), respectively, which were isolated from *Bacillus* sp. UST050418-715 collected from sponge in the sea near St. Juan Island, Washington, USA [51]. Compound **25** was also found from sponge-endosymbiotic *Bacillus* species collected from Agatti island located in the Arabian Sea, in the Laksha Archipelago of India [52].

4. Linear Lipopeptides

Linear lipopeptide is a kind of lipopeptide, in which amino acids are connected in turn into linear, unconnected head and tail and no cyclic structure. Fatty acids are connected to α-amino groups or other hydroxyl groups at the N-terminal of the peptide chain [53]. **Figure 4** lists the structures of linear lipopeptides that were produced by marine-derived *Bacillus* species.

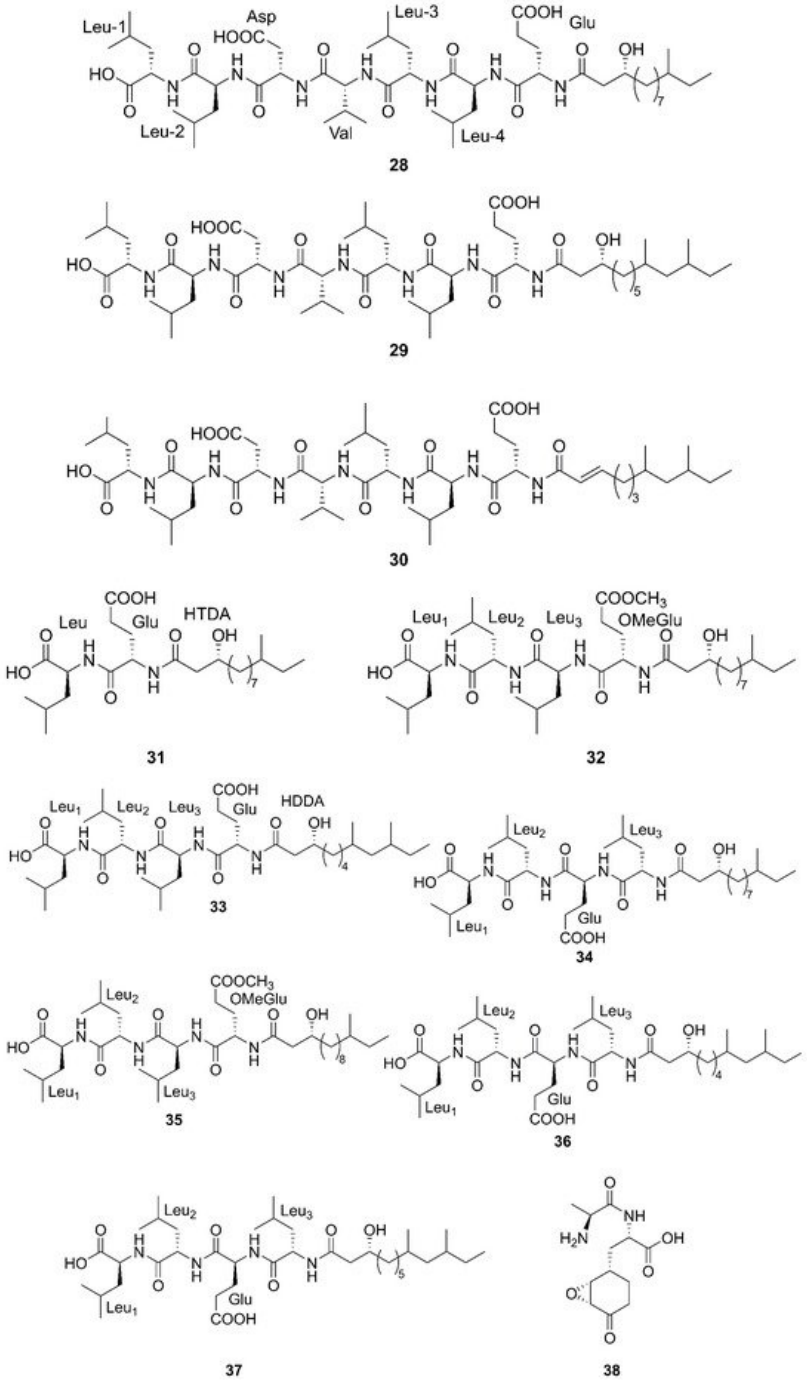

Figure 4. Linear lipopeptides produced by marine-derived *Bacillus* species.

Three newfound linear lipopeptides named gageostatins A (**28**), B (**29**) and C (**30**), comprising of hepta-peptides and new 3-*β*-hydroxy fatty acids yielded by a marine-derived bacterium *B. subtilis* from the culture broth [35]. Furthermore, three novel linear lipopeptides possessing di- and tetrapeptides and a new fatty acid, gageotetrins A (**31**), B (**32**) and C (**33**), were isolated from a marine *B. subtilis* [54]. Four unreported lipopeptides, gageopeptides A (**34**), B (**35**), C (**36**), and D (**37**) were isolated and identified from a marine-derived bacterium *B. subtilis*, which consisted of tetrapeptides and 3-*β*-hydroxy fatty acids [55]. The fatty acid of **28**, **31**, **32** and **34** was identical and determined as a 3-*β*-hydroxy-11-methyltridecanoic acid. Likewise, compounds **29** and **37** both possessed the same fatty acid, 3-*β*-hydroxy-9,11-dimethyltridecanoic acid. Moreover, the fatty acid unit of **33** and **36** was 3-*β*-hydroxy-8,10-dimethyldodecanoic acid. In particular, the absolute stereochemistry at C-3 of the fatty acids of linear lipopeptides **28**–**37** is *R* configuration except **30**. Additionally, the configuration of the amino acid residues in **28**–**37** was found to be *L*-form, while Val in **28**–**30** was *D*-form. Besides, bacilysin (**38**), another identified dipeptide, was isolated from seaweed-associated *B. amyloliquefaciens* MTCC 10456 in Microbial Type Culture Collection and Gene Bank (MTCC) of Chandigarh in India. Notably, this is the first report on the co-production and isolation of anti- *Malassezia* spp. chemicals from marine *Bacillus* species [41]. In conclusion, all linear Lipopeptide mentioned above were obtained from the Gageocho in the southern reef (Republic of Korea) except **38**.

5. Nonribosomal Peptides

Nonribosomal peptides (NRPs) are large enzyme complexes with a modular structure responsible for binding a particular amino acid. NRPSs of *Bacillus* are synthesized by large multimodular nonribosomal peptide-synthetase (NRPS) through prolonging the active monomers of amino acid building blocks [56]. **Figure 5** lists the structures of nonribosomal peptides produced by marine-derived *Bacillus* species.

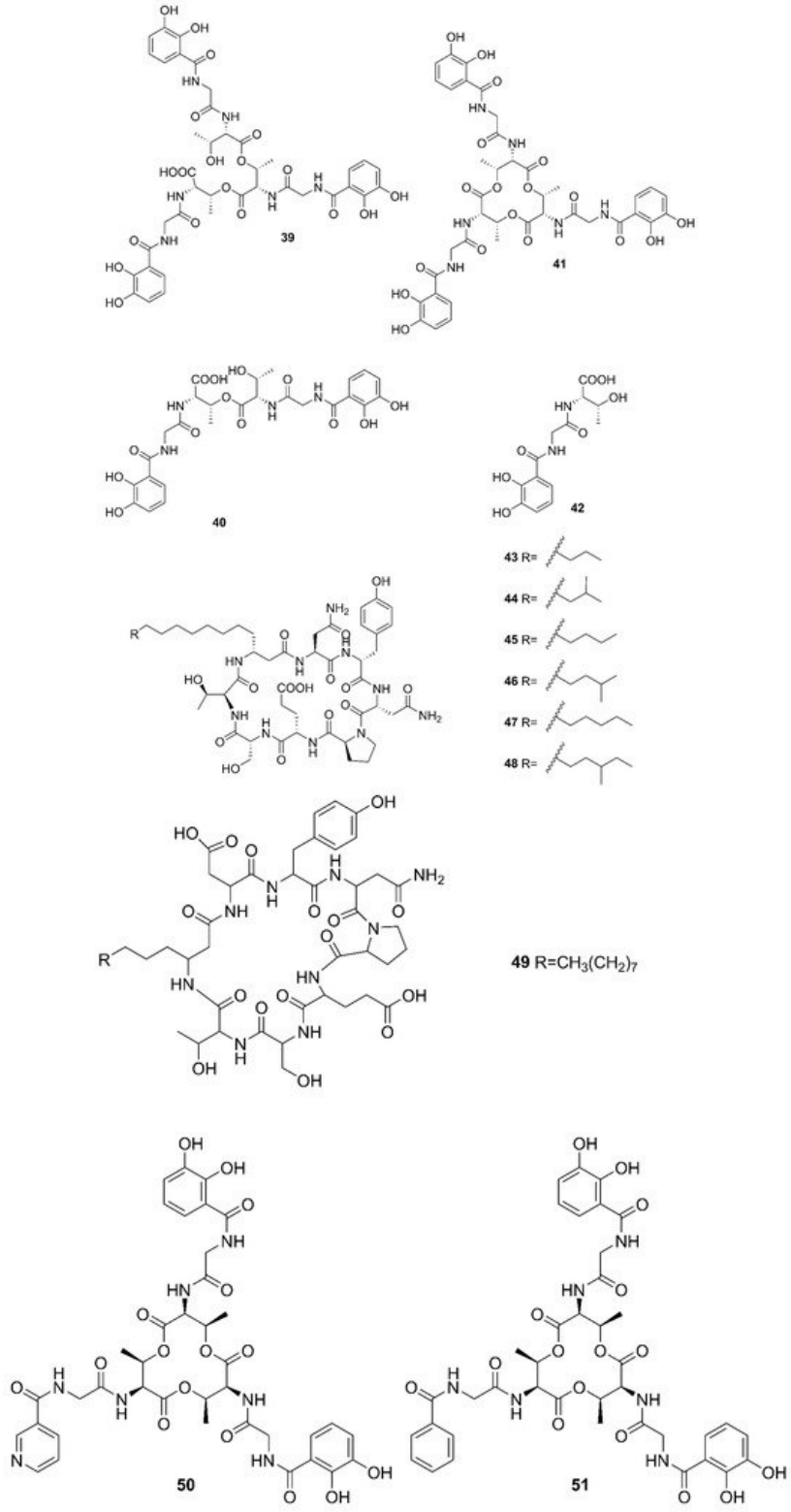

Figure 5. Nonribosomal peptides produced by marine-derived *Bacillus* species.

Two unreported compounds, bacillibactin B (**39**) and bacillibactin C (**40**), along with the known compounds Bacillibactin (**41**) and S_{VK21} (**42**), were discovered from *Bacillus* sp. named PKU-MA00093 from sponges, corals and sediments in the South China Sea. Additionally, compounds **43**–**48** were characterized as bacillomycin D, *iso*-C15 bacillomycin D, C15 bacillomycin D, *iso*-C16 bacillomycin D, C16 bacillomycin D, and *anteiso*-C17 bacillomycin D, respectively. They were isolated from *Bacillus* sp. PKU-MA00092 collected from sponges, corals and sediments in the South China Sea. Notably, this was the first time to report the structures of **45** and **47** with fully specified ^{1}H NMR and ^{13}C NMR data; their structures are highly similar except for the fatty acid moieties [57]. Compounds **45** and **47** in company with C14 bacillomycin D (**49**),

were obtained from seaweed-associated *B. amyloliquefaciens* MTCC 10456 collected from seaweed in the MTCC, of Chandigarh, India [41]. Moreover, compounds **45** and **49** were also isolated from the methanol extract harvested from marine-derived *B. megaterium* CGMCC7086 obtained from the intestines of marine fish in the Yellow Sea of East China by two-step ultrafiltration and liquid chromatography-electronic spray ionization-tandem mass spectrometry (LC-ESI-MS/MS). Using a highly-efficient separation technique and identification method, more than 40 lipopeptides variants were identified from a *Bacillus* strain [23]. Besides, compound **47** was isolated from *B. subtilis* B38 strain [58]. Two unique bacillibactins, bacillibactins E (**50**) and F (**51**) were the first bacterial siderophores containing nicotinic and benzoic acid moieties isolated from a marine sponge *Cinachyrella apion* associated *Bacillus* sp. WMMC1349 collected from the west shore of Ramrod Key in Florida [24].

6. Polyketides

Polyketides are a class of extremely large secondary metabolites assembled from simple acyl-coA compounds [59]. *Bacillus* species of marine origin was a potential source of bioactive compounds of polyketides and bacteriocins with significant antimicrobial activity against human pathogens [60]. **Figure 6** lists the structures of polyketides that were produced by marine-derived *Bacillus* species.

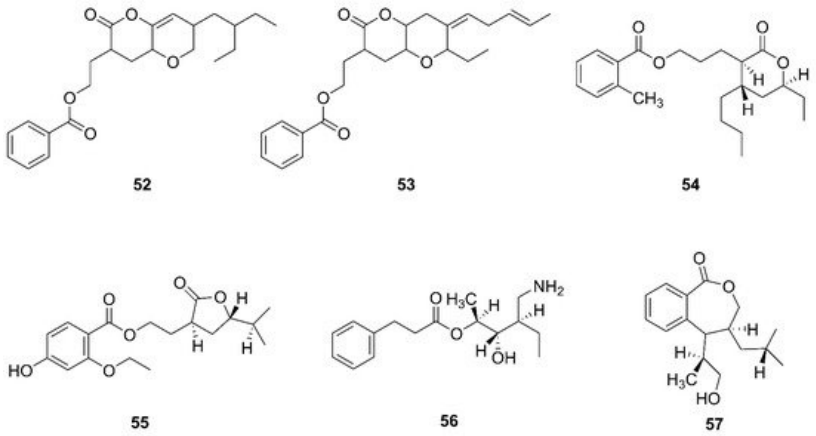

Figure 6. Polyketides produced by marine-derived *Bacillus* species.

Two novel compounds, O-heterocycle pyrans, 2-(7-(2-Ethylbutyl)-2,3,4,4a,6,7-hexahydro-2-oxopyrano-[3,2b]-pyran-3-yl)-ethyl benzoate (**52**) and 2-((4Z)-2-ethyl-octahydro-6-oxo-3-((E)-pent-3-enylidene)-pyrano-[3,2b]-pyran-7-yl)-ethyl benzoate (**53**) were obtained by repeated chromatography from the heterotrophic bacterium *B. subtilis* MTCC 10407 associated with brown seaweed *Sargassum myriocystum* on the southeast coast of India [61]. Additionally, 11-(15-butyl-13-ethyl-tetrahydro-12-oxo-2H-pyran-13-yl) propyl-2-methylbenzoate (**54**), 9-(tetrahydro-2-isopropyl-11-oxofuran-10-yl)-ethyl-4-ethoxy-2-hydroxybenzoate (**55**), 12-(aminomethyl)-11-hydroxyhexanyl-10-phenylpropanoate (**56**), and 7-(14-hydroxypropan-13-yl)-8-isobutyl-7, and 8 dihydrobenzo[c]oxepin-1(3H)-one (**57**) were isolated from a heterotrophic marine bacterium *B. amyloliquefaciens.* This strain was isolated from the brown seaweed *Padina gymnospora* collected from the intertidal zone of the Mannar Gulf in Peninsular India [60].

7. Macrolactins

Marine *Bacillus* species produce abundant polyketide classes of antibiotic agents, such as macrolactins, difficidins, and bacillaenes [13][36][62]. Diffcidin is a highly unsaturated macrocyclic polyene with a 22-membered carbon skeleton and a phosphate moiety, which is rarely found in secondary metabolites of *Bacillus* species. Bacillaene is a linear structure consisting of a conjugated hexaene. Carbon skeleton of most macrolactins contains three diene groups attached to the carbon backbone of a 24-membered lactone ring [36]. **Figure 7** lists the structures of macrolactins produced by marine-derived *Bacillus* species.

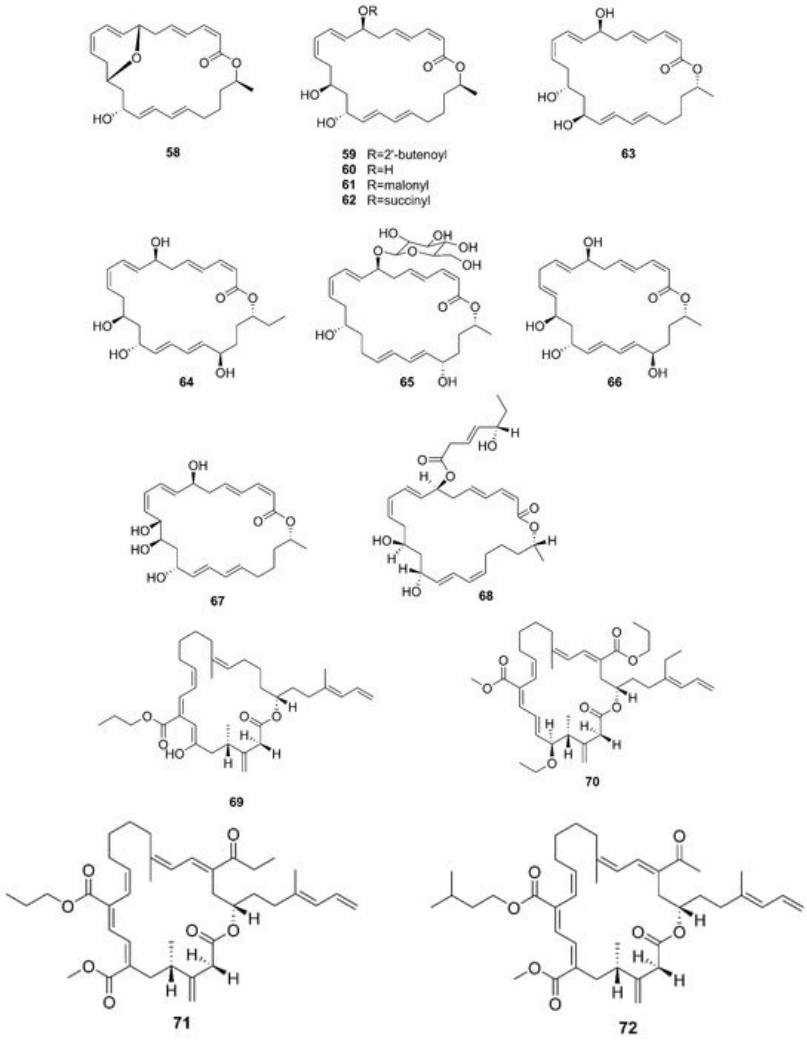

Figure 7. Macrolactins produced by marine-derived *Bacillus* species.

A new macrolactin derivative, 7,13-epoxyl-macrolactin A (**58**), along with four known macrolactins, 7-O-2′E-butenoyl macrolactin A (**59**), Macrolactin A (**60**), 7-O-malonyl macrolactin A (**61**), and 7-O-succinyl macrolactin A (**62**) were isolated from bacteria *B. subtilis* B5. It is worth emphasizing that this strain was extracted from deep-sea sediments at depths of 3000 m in the Pacific Ocean [63]. Compounds **60** and **62** were also isolated from seaweed-associated *B. amyloliquefaciens* MTCC 10456 in the MTCC of Chandigarh, India; this is the first report on the co-production and isolation of anti-*Malassezia* spp. compounds from marine *Bacillus* species [41]. In particular, the major difference between compounds **58** and **59**–**62** is in the epoxy ring. Compound **58** displayed a potent inhibitory effect on the expression of interleukin-1*β* (IL-1*β*), interleukin-6 (IL-6) and inducible nitric oxide synthase (iNOS), due to the existence of the epoxy ring [63]. Five novel 24-membered macrolactins named bamemacrolactins A (**63**), B (**64**), C (**65**), D (**66**) and E (**67**) were produced by *B. siamensis,* which was isolated from the gorgonian coral *Anthogorgia caerulea* gathered from Beihai city (Guangxi, China) [64]. The 7-O-methyl-5′-hydroxy-3′-heptenoate−macrolactin (**68**), a new macrolactin compound, was obtained from *B. subtilis* MTCC10403 associated with seaweed *Anthophycus longifolius* collected from the Gulf of Mannar of Peninsular India [65]. Compounds **69**–**72** were characterized as four homologous difficidin-type 21-membered macrocyclic lactone, isolated from a heterotrophoic *B. amyloliquefaciens* MTCC12713 associated with an intertidal macroalga *Kappaphycus alverezii* collected from the Gulf of Mannar in Peninsular India. In addition, they were established as 18,19-dihydro-6-hydroxy-8-propyl carboxylate difficidin, 5-ethoxy-28-methyl-(9-methyl-19propyl dicarboxylate) difficidin, (6-methyl-9-propyl dicarboxylate)-19-propanone difficidin, and 20-acetyl-(6-methyl-9-isopentyl dicarboxylate) difficidin, respectively [13].

8. Other Compounds

Figure 8 lists the other compounds produced by marine-derived *Bacillus* species. A novel thiopeptide named micrococcin P3 (**73**) and a known compound named micrococcin P1 (**74**) were isolated from the fermentation broth of *B. stratosphericus* [66]. Five new bacillamidins A (**75**), B (**76**), C (**77**), D (**78**) and E (**79**), along with two known synthetic analogs, bacillamidins F (**80**) and G (**81**), were isolated from the marine-derived *B. pumilus* strain RJA1515. This strain was extracted from deep-sea sediments at depths of 84 m collected in Bamfield in British Columbia [67]. Ieodoglucomide C (**82**) and ieodoglycolipid (**83**), two new glycolipids, were produced by the marine-derived *B. licheniformis* 09IDYM23 which

was isolated from sediments at a depth 20 m collected at Ieodoin the southern reef of the Republic of Korea, both of which were obtained from the fermentation of this strain [68]. According to bioactivity-guided strategy, (-)-sattabacin (**84**) and (-)-4-hydroxysattabacin (**85**) were firstly discovered from *Bacillus* sp. (SCO-147) collected from marine sediments in Suncheon Bay of Korea [69]. Marine-derived *B. subtilis* AD35, gathered from marine water and sediment at the Alexandria sea shore in Egypt, could yield a previously reported but firstly isolated compound, Di-(2-ethylhexyl) phthalate (DEHP) (**86**) [70]. Additionally, compound **86** and dibutyl phthalate (DBP) (**87**) were isolated from the extract broth of marine-derived *B. polymyxa* L_1-9, which was collected in a mud sample from the intertidal mudflat in the Lianyungang Port of China [71].

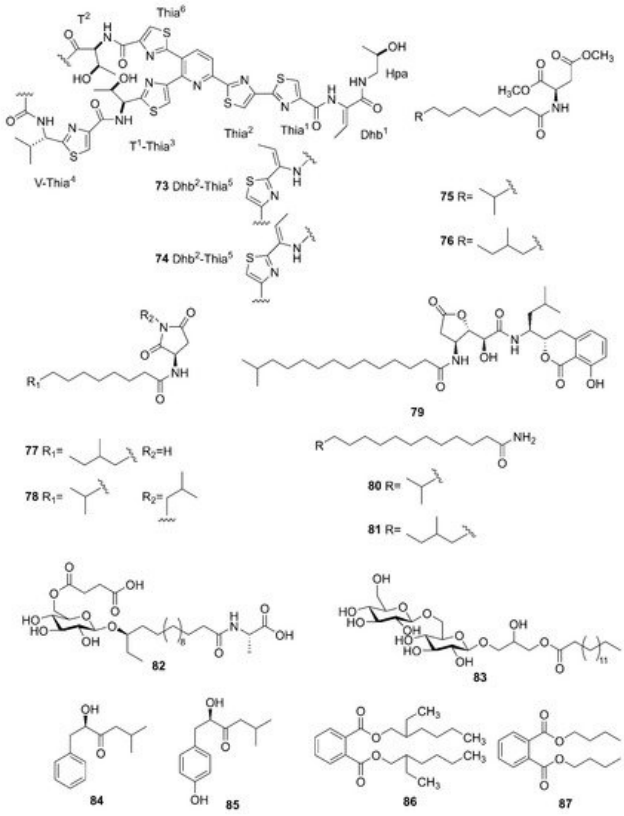

Figure 8. Other compounds produced by marine-derived *Bacillus* species.

A total of 87 secondary metabolites were reported from marine-derived *Bacillus* species from January 2014 to December 2021. Their chemical structures were classified into cyclic lipopeptides (**1**–**19**, among them, **1**–**2** surfactins, **3**–**10** belong to iturins, **11** belongs to plipastatin), diketopiperazines (**20**–**27**), linear lipopeptides (**28**–**38**), nonribosomal peptides (**39**–**51**), polyketides (**52**–**57**), macrolactins (**58**–**72**, among them, **69**–**72** belong to difficidins), and other compounds (**73**–**87**) according to their putative biogenetic sources. As shown in **Figure 9**A, 21.84% of the compounds reported were CLPs, and these compounds account for an overwhelming majority of all 87 metabolites, followed by macrolactins with 17.24%. Therefore, CLPs are a class of secondary metabolites with structural diversity and pharmacological perspective.

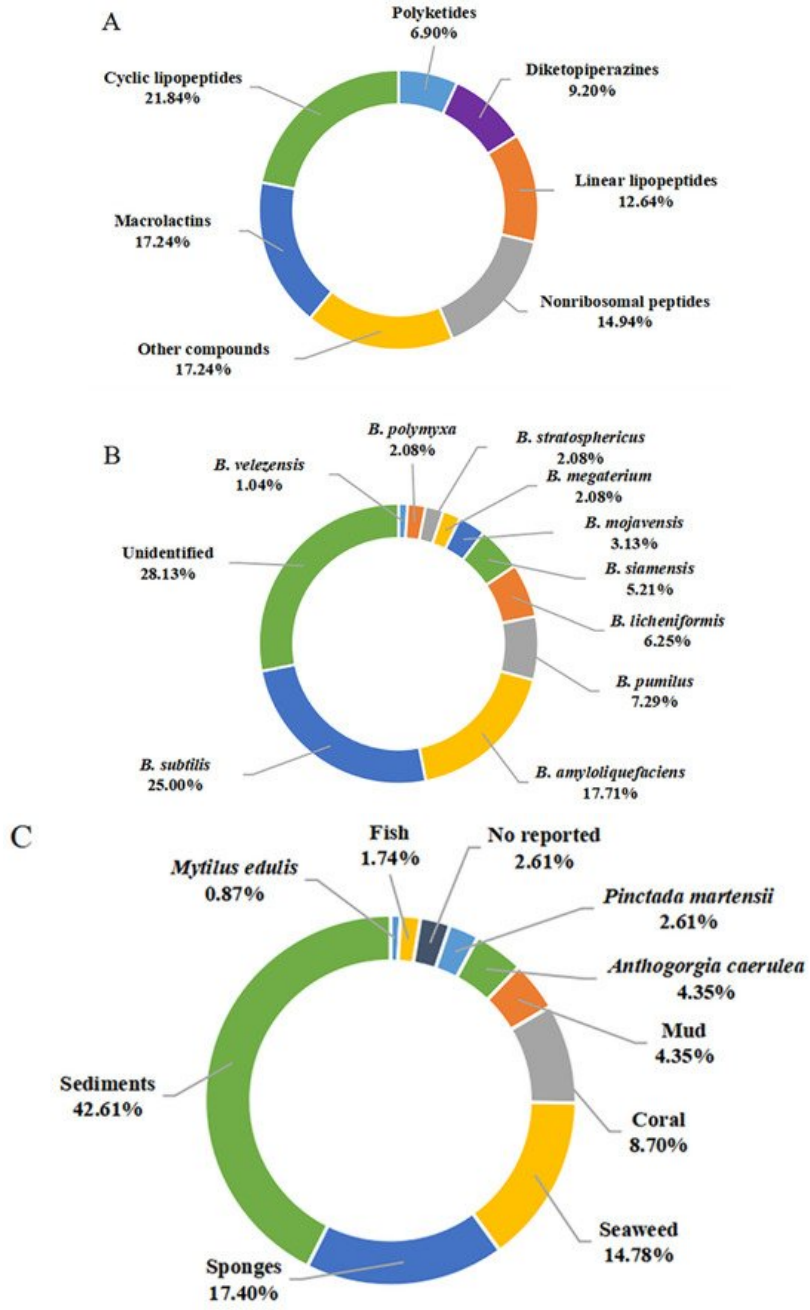

Figure 9. Quantification of studies on secondary metabolites from marine-derived *Bacillus*: (**A**) Chemical structures categories; (**B**) Producing strains; (**C**) Environment sources.

The genus *Bacillus* comprises more than 350 species, some of which are used as antifungal agents, while others are promising producers of green pesticide [14]. As discussed above, a total of 10 identified species, including *B. subtilis*, *B. amyloliquefaciens*, *B. megaterium* CGMCC7086, *B. mojavensis* B0621A, *B. licheniformis*, *B. siamensis*, *B. stratosphericus*, *B. pumilus* RJA1515, *B. polymyxa* L_1-9, and *B. velezensis* SH-B74 were reported as the producing strains of these described secondary metabolites. Among them, *B. subtilis* and *B. amyloliquefaciens* were the most prolific strains, with 24 (20.00%) and 17 (17.71%) metabolites identified, respectively (**Figure 10**B). CLPs are ubiquitous in several *Bacillus* strains. However, linear lipopeptides are found predominantly in *B. subtilis* species, while the macrolactins are more preponderant in *B. amyloliquefaciens* species, suggesting the species-specific metabolites.

The secondary metabolites of marine-derived *Bacillus* species could be isolated from marine sediments, marine invertebrates (sponges, molluscs, and corals), and vertebrates (mainly fishes), as well as marine plants (mainly seaweed). Currently, there are 9 reported sources of *Bacillus* secondary metabolites. As shown in **Figure 9**C, a total of 49 compounds {**1**–**7**,**11**,**15**–**18**,**28**–**37**,**39**–**48**,**58**–**62**,**75**–**85**,**86** (*B. subtilis* AD35)} originated from marine sediments, accounting for 42.61% of the sources of *Bacillus* species. In particular, the producing strains of **58**–**62** originated from deep-sea sediment at a depth of 3000 m, while the other strains of **75**–**83** originated from deep-sea sediment at depths less than 100 m. Moreover, the producing strains of **12**–**14, 86** (*B. polymyxa* L_1-9), and **87** originated from mud. More precisely, the producing strains of **15**–**16** and **28**–**37** originated from the Republic of Korea's southern reef. Twenty compounds (**20**–**27**,**39**–**48,50,51**), identified from marine sponges, accounted for 17.40% of the reported environmental sources of *Bacillus* secondary metabolites. It is worth noting that **20** belonging to diketopiperazine were isolated

unprecedentedly from a sponge-associated microbe. Moreover, **45**–**49**, **52**–**56** and **63**–**67** were also derived from coral, wherein **63**–**67**, whose producing strains were obtained from the gorgonian coral *A. caerulea*, accounted for 4.35% of the reported environmental sources of *Bacillus* secondary metabolites. The **8**–**10** and **19** that originated from pearl oyster *P. martensii* and *M. edulis*, respectively, accounted for 3.48% of the reported ones. A total of 17 secondary metabolites {**38,45**,**47**,**49**,**52**–**57**,**60**,**62** (*B. amyloliquefaciens* MTCC 10456) and **68**–**72**} were identified from *Bacillus* residing in marine plants, accounted for 14.78% of the reported total amount. Thereinto, the producing strains of **52**–**57** originated from brown seaweed, while the producing strains of **45**,**47**,**49**,**60**,**62** (*B. amyloliquefaciens* MTCC 10456), **38**,**52**–**57** and **68**–**72** were collected from seaweed. In addition to these producing strains, only one *Bacillus* strain (*B. megaterium* CGMCC7086), which produced **45** and **49**, was obtained from the intestines of marine fish and accounted for 1.74% of the reported total amount. Unfortunately, the environmental sources of the producing strain of **47** (*B. subtilis* B38), **73** and **74** (*B. stratosphericus*) were not described. From the above analysis, it can be concluded that marine sediments and sponges are more abundant sources of productive strains of marine-derived *Bacillus*, and which deserved much more attention in subsequent chemical studies.

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