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New secondary metabolites of the marine microorganisms isolated from Mariana trench sediment

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Abstract
Due to the exceptional topographical situations, Mariana trench's sediment can be a unique habitat for deep-sea microorganisms with the talent to produce structurally differentiated secondary metabolites. It leads to the production of new novel bioactive metabolites for drug discovery. This review mainly provides on the summary of secondary metabolites with biological activities isolated from deep-sea fungi and bacteria in the Mariana trench sediments during 2010-2021. Effective technical route and experimental plan for screening and obtaining natural active compounds from deep sea microorganisms are also summarized in this review. Mariana trench can be regarded as a source of unexplored and new chemical diversity for drug discovery because numerous new novel compounds have been discovered by researchers within only a few studies. The number of twenty-nine new secondary metabolites have been discovered from microorganisms in Mariana trench's sediment. Among them, fourteen new phenazine compounds are isolated from *Dermacoccus abyssi* sp. nov., strains MT1.1 and MT1.2 [14,27,31-32] and four new tetramic acids from *Cladosporium sphaerospermum* L3P3 [26], one new meroterpenoid from *penicillium* sp. SY2107 [22], three new pyrrole alkaloids from *Bacillus subtilis* SY2101 [23], one new novel salicylamide analogue, two new diketopiperazine derivatives, one new phenylethanediol from *Streptomyces* sp. SY1965 [21], three new polyketides from *Phoma* sp [30], respectively.

Keywords: mariana trench, secondary metabolites, microorganisms, deep-sea

Introduction
Secondary metabolites (SMs) are natural products synthesized mainly by bacteria, fungi and plants. They are molecules of low molecular weight with diverse chemical structures and biological activities. According to the Breinbauer *et al*. 2002 [1], secondary metabolites (SMs) are the molecules with a molecular weight ranging between 100 and 1000 Da. The antibiotic was also defined as a "secondary metabolite by Selman Waksman in 1941 [25]. However, not all secondary metabolites serve as antibiotics; many of them serve as plant growth factors and enzyme inhibitors [2] and as self-regulating factors in some bacteria (e.g. A-Factor) [3] and fungi (e.g. butyrolactone I) [4].
The major sources of secondary metabolites are plants, bacteria, fungi, and many marine organisms (sponges, tunicates, corals, and snails). Over 2,140,000 secondary metabolites are known and are commonly classified according to their vast diversity in structure, function, and biosynthesis. There are five main classes of secondary metabolites such as terpenoids and steroids, fatty acid-derived substances and polyketides, alkaloids, nonribosomal polypeptides, and enzyme cofactors. [5] The search for new pharmacologically active agents obtained by screening natural sources has led to the discovery of many clinically useful drugs that play a major role in the treatment of human diseases. Approximately 60% of the antitumor and anti-infective agents that are commercially available or in late stages of clinical trials today are of natural product origin. Natural products are still major sources of innovative therapeutic agents for infectious diseases (both bacterial and fungal), cancer, lipid disorders and immunomodulation [24].
Microbial secondary metabolites, like antibiotics, pigments, growth hormones, antitumor agents and others, are not essential for the growth and development of microorganisms, but they have shown a great potential for human and animal health. The microorganisms which are capable of the above-mentioned compounds including bacteria, Actinobacteria and fungi produce a diverse array of bioactive small molecules with significant potential to be used in medicine. These metabolites, otherwise known as bioactive substances, are profoundly used as antibiotics and may be effective against infectious diseases such as HIV-1 [6], conditions of multiple bacterial infections (penicillin, cephalosporins, streptomycin, and vancomycin), or neural tube defects and neuropsychiatric sequelae. [7-8] Terrestrial plants have been used for centuries in the treatment of human diseases, whereas the exploration of microorganisms as a source of therapeutical compounds has a relatively short history. [9] In spite of that, more than 10% of the current natural bioactive products have a microbial origin [10].
Marine microbes live in a biologically competitive environment with unique conditions of pH, temperature, pressure, oxygen, light, nutrients and salinity, which is especially rich in chlorine and bromine elements. The ecology of marine natural products actually reveals that many of these compounds are chemical weapons and

have evolved into highly potent inhibitors of physiological processes in the prey, predators or competitors of the marine organisms that utilize them for survival. There is no wonder that marine microbial metabolites exhibit special biological activities compared with 'terrestrial' bacteria. [11-12] Blunt *et al.* (2004) [11] listed that in marine environment sponges (37%), coelenterates (21%) and microorganisms (18%), are major sources of biomedical compounds, followed by algae (9%), echinoderms (6%), tunicates (6%), molluscs (2%) bryozoans (1%), *etc.* [11] More than 20 000 bioactive metabolites produced by marine microorganisms have been reported, and almost 10 000 are derived from actinomycetes, mainly of *Streptomyces* species[12]. Most of these metabolites are potent antibiotics; thus, streptomycetes have become a primary source of natural antibiotics for pharmaceutical and industrial applications [12]. However, marine microorganisms have not been given the attention they deserve and a very limited insight into the capabilities and bioactive potential of marine microorganisms is available in literature to date. The huge biomedical potential of marine microorganisms remains mostly unexplored, and the wide chemical diversity of these microbial-derived products offers the possibility to modulate multiple molecular targets [13].

Antibiotic compounds are the weapons of chemical warfare among microorganisms. It is in the process of evolution that these compounds have evolved, allowing the survival of the fittest, or survival of the most prolific producer of toxic compounds. The fight for a territory is a reality not only for animals, but for microorganisms as well. The means to do this vary among the microbes, from finding an own environmental niche (as in the example of extremophiles) to producing secondary metabolites that kill intruders (as in antibiotics). The antibiotic compounds discovered from microorganisms revolutionized modern medicine when used as a weapon against bacterial infections. Microbes have a long history of use in the treatment of cancer. Microbial metabolites are among the most important of the cancer chemotherapeutic agents. From the 22,500 biologically active compounds that have been obtained so far from microbes, 45% are produced by actinomycetes, 38% by fungi and 17% by unicellular bacteria [12].

Significance of deep sea microorganisms for secondary metabolites

Microbial antibiotics have been in use in medicine since the 1940's. Antibiotics decreased our vulnerability to common bacterial infections that had earlier been death sentences. The following over-use of antibiotics can, therefore, be easily understood. Unfortunately, the evolution of pathogenic microbes did not abruptly end, as all microbes carrying biosynthetic genes for a certain antibiotic, carry also resistance genes for the same compound; otherwise the organisms had not survived the production of their own antibiotics [18].

The ocean is the mother of life and it is believed that the most primitive forms of life originated from this "primordial soup". It harbors a vast variety of marine organisms that are diverse in their physiology and adaptations [20].

The deep-sea is one of the less explored and extreme environments on Earth. The deep sea was assumed as a biological desert, because of extreme variations in pressure, salinity, and temperature. These special environment variables may lead to producing distinct chemical entities with diverse biological activities. Therefore, the deep sea marine microbes having immense genetic and bio-chemical diversity have become a tremendous source of novel effective drugs. It was reported that about 75% of deep –sea natural products have biological activity, about 40% are drug-like, and 2/3 are within Known Drug Space (KDS). [17]

The role of Mariana Trench sediments for marine microorganisms

Mariana Trench, located in the western Pacific Ocean, is known as the deepest trench in the world, within which the Challenger Deep, at its southernmost end, is the deepest point on Earth [1, 28]. Its depth is variously reported to be 10 915 to 10 920 m, corresponding to about 110 MPa of hydrostatic pressure [14-15]. Due to the unique geographical location and environment, it is regarded to be a unique ecosystem, which is the habitat for deep-sea microorganisms with the ability to produce structurally diversified secondary metabolites [16]. In contrast to the other trenches located in the North-West Pacific region, the Mariana Trench is topographically isolated from other trenches by the impinging Ogasawara Plateau and Caroline Ridge [19]. Thus, these topographical barriers may interrupt the transfer of organic compounds and (micro-) organisms entrained by inter trench currents. Mariana Trench sediments are enriched in microorganisms, whereas, the structures and bioactivities of their secondary metabolites are meager and should have a priority to be explored. Nowadays, the recent advancements in marine technologies have allowed human-beings to access the deep sea and have led to the detection of microbial activities even in the Marina Trench with a depth of 10000 m.

Objectives

This aims to enable researchers to better understand the research work in these fields and to provide the future analysis.

To reach the goal, this article summarized the characteristics of secondary metabolites isolated from the marine microorganisms in Mariana Trench sediments, their biological activities and research methods.

The common technical method for the study of secondary metabolites from the marine microorganisms isolated from Mariana Trench sediments

1. Sediment samples are collected from the Mariana Trench at certain depth with the sediment sampler or sediment corer. The samples are passed through a sieve (1.7 mm mesh) to remove large pieces of debris and

vegetation. The sediment is air dried at 28˚ C for 7 days and the dried sample (1.0 g) is diluted with sterile water to make dilutions of 10^{-2}, 10^{-3}, and 10^{-2} g/mL.

2. Each dilution (200µL) is covered on the surface of different media such as B, BY, D, DY, E, EY, ISP2, ISP2Y, ISP4, and ISP4Y etc. in Petri dishes and then incubated at 28˚C for 14 days.
3. The pure strains are identified by internal transcribed spacer (ITS) rDNA sequence analysis and the ITSrDNA sequence of strain is compared to those in the Genbank using nucleotide BLAST (Basic Local Alignment Search Tool).
4. For small scale fermentation and extraction, pure strains on solid medium are transferred into a 500 ml Erlenmeyer flask containing 250 ml of liquid different medium. These different strain liquid medium are carried out on a shaking incubator with 180 rpm, 28C for 2 weeks.
5. The liquid media in small bottles are filtered under vacuum using a Buchner funnel and discard the mycelium residue. The liquids are transferred the culture filtrate into a separation funnel and separated the EtOAc and H2O phases and extracted the aqueous phase three times with 300 ml EtOAc each. the EtOAc extracts are dried under vacuum (~200 mbar) using a rotary evaporator at 40 °C to give a solid or oily residue.
6. At the same time, for small scale rice medium, the seed broths of liquid medium which are inculated for 3 days in a shaker are transferred into the solid rich medium flask (210g) and are incubated for 4 or 6 weeks at room temperature under static condition and daylight.
7. For the purposes of rice medium culture extraction, the rice medium fermentation flasks are ended by adding 250 ml EtOAc to each culture flask. Before that, the culture medium is cut containing the mycelium into small pieces to allow exhaustive extraction with EtOAc and agitated the flask and left the flasks closed for at least 24 hr. The contents are filtered under vacuum using a Buchner funnel and repeat the extraction 3 times with EtOAc until exhaustionan.
8. In order to select the suitable media that allow the growth of the bacterial strains and high production of bioactive secondary metabolites, the resulting crude extracts from different medium are dissolved in 1 ml methanol. Antimicrobial activity of each extract is determined using the agar disc diffusion assay. 100-300 µg of crude extract was applied onto 6 mm filter paper discs.
9. Large scale fermentation and extraction is carried out the same manner as described for small scale by the use of one suitable medium.
10. The crude extracts often contain a mixture of many components in a complex matrix. The components need to be separated from each other so that each individual component can be identified by other analytical methods. Therefore, initially thin layer chromatography conduct for each fraction prior to further chemical work, to monitor the identity of each and the qualitative purity of the fractions or the isolated compounds. Band separations in TLC ware also very helpful in optimizing the solvent system that would be later applied for column chromatography.
11. For an ideal pre-treatment of large amount of samples prior to fine chromatography separation like Lobar column or HPLC separations, and vacuum liquid chromatography (VLC) technique run as a column.
12. Fractions derived from VLC were subjected to repeated separation through series of column chromatography using appropriate stationary and mobile phase solvent system previously determined by TLC. Purification of fractions was later performed on semi-preparative HPLC.
13. The purification procedures continue until compound of sufficient purity is obtained to allow structural elucidation.
14. Structure elucidation is carried out using various spectroscopic methods, mainly MS and NMR (1 d and 2 d). For the elucidation of the absolute configuration of new chiral natural products, derivatization methods such as the preparation of Mosher esters or by using Marfey's method are sometimes necessary (alternatively, the absolute configuration may be elucidated by X-ray crystallography or by CD spectroscopy followed by quantum chemical calculations).
15. For specialized screening bioassays, crude extracts and pure compounds is tested for antibacterial activity against the following standard strains: gram positive bacteria *Bacillus subtilis* and *Staphylococcus aureus*, gram negative bacteria *Escherichia coli*. Three fungal test strains were applied for antifungal activity: *Saccharomyces cerevisiae*, *Candida albicans*, and *Cladosporium herbarium*. The agar diffusion assay was performed according to the Kirby-Bauer Test (Bauer *et al*., 1966) and test other cytotoxicity.

New secondary metabolites isolated from the marine microorganisms in Mariana Trench sediments

Abdel-Mageed *et al* 2010 have correctly observed seven new oxidized and reduced phenazine-type pigments, dermacozines A–G, a new family of phenazine compounds together with the known phenazine-1-carboxylic acid and phenazine-1,6-dicarboxylic acid produced by *Dermacoccus abyssi* sp. nov., strains MT1.1 and MT1.2 isolated from Mariana Trench sediment at a depth of 10898 m, using ISP2 and 410 media fermentation (figures. 1-4). The continuing study by Wagner *et al* 2014 observed three new pigmented heteroaromatic phenazine compounds, dermacozines H–J [14, 27] (figures. 5-7) Subsequently, another four new dermacozine derivatives were isolated from *Dermacoccus abyssi* MT 1.1 in Mariana Trench sediment. It is reported as dermacozine M by Abdel-Mageed *et al* 2020 and dermacozines N–P by Juhasz *et al* 2021 [31-32] (figures. 4, 8-10)

Dermacozine A is fluorescent yellowish green powder and the molecular formula is $C15H14N4O_2$ [14] (figure. 1) Dermacozine B is reddish brown powder and the molecular formula is $C_{22}H_{18}N_4O_3$.[14] (figure. 2) Dermacozine C

is a reddish-brown substance and the molecular formula is $C_{22}H_{17}N_3O_4$. [14] (figure. 2) Dermacozine D is an optically active golden yellow substance and the molecular formula is $C_{24}H_{19}N_3O_5$. [14] (figure. 3) Dermacozine E is a bluish violet substance and the molecular formula was determined as $C_{23}H_{16}N_4O_3$. [14] (figure. 4) Dermacozine F is a bluish violet substance and the molecular formula is $C_{23}H_{15}N_3O_4$. [14] (figure. 4) Dermacozine G is a bluish violet substance and the molecular formula is $C_{23}H_{15}N_3O_5$ [14] (figure. 4) Dermacozine H is an orange-brown powder and the molecular formula is C16H13N3O4. [27] (figure. 5) Dermacozine I is a dark-pink powder and the molecular formula is $C_{22}H_{18}N_4O_3$. [27] (figure. 6) Dermacozine J is a yellow-orange powder and the molecular formula is $C_{27}H_{24}N_5O_6S$. [27] (figure. 7)

Dermacozine C exhibits the strongest radical scavenging activity (IC_{50} 8.4 µM) followed by Dermacozine H-J and Dermacozine B (IC_{50} 18.8 µM, IC_{50} 19.6 µM, IC_{50} 34.6 µM, IC_{50} 38.0 µM and while dermacozines A and D had the weakest antioxidant activity (IC_{50} 77.5 and 106.9 µM, correspondingly. [27] Wagner *et al* 2014 (*Z*)-*N*-(4-hydroxystyryl) formamide exhibits moderate antiproliferative activity against human glioma U251 and U87MG cells with IC_{50} values of 17.0 ± 2.9 and 39.8 ± 1.6 µM, respectively. Abdel-Mageed *et al* 2010 provided that dermacozines A–E show cytotoxic activity against K562 cells (human chronic myelogenous leukemia cells) at a low µM range whereas, dermacozines F and G was the highest cytotoxic potency with IC_{50} values of 9 and 7 µM, respectively [27].

Dermacozine M is a navy blue powder and the molecular formula is C30H20O4N4.[31] (figure. 4) Dermacozine N is a pink amorphous powder and the molecular formula is $C_{21}H_{15}O_3N_5$.[32] (figure. 8) Dermacozine N bears a novel linear pentacyclic phenoxazine framework [32]. It was the first natural linear pentacyclic oxazinophenazine for natural product. The cytotoxic activity of dermacozine N shows against a panel of five human tumor cell lines: human melanoma (A2058) and hepatocellular human carcinoma cell lines (HepG2) exhibiting weak activity, with IC_{50} values of 51 and 38 µM, respectively. Besides, dermacozine N is a suitable compound for further research in the field of photodynamic therapy due to the NIR absorption maxima which would inhibit less with the tissue absorption maxima. Dermacozine O is an ink-blue amorphous powder and molecular formula is $C_{23}H_{15}O_4N_3$ [32]. (figure. 9) Dermacozine O is a constitutional isomer of dermacozine F. Dermacozine O displays no cytotoxic activity when tested against A549 (lung carcinoma), A2058 (metastatic melanoma), MCF7 (breast adenocarcinoma), MIA PaCa-2 (pancreatic carcinoma), and HepG2 (hepatocyte carcinoma) cell lines. Dermacozine P is a purplish amorphous powder and molecular formula is $C_{21}H_{13}O_4N_3$ (figure. 10). Dermacozine P is 8-benzoyl-6-carbamoylphenazine-1-carboxylic acid [32].

Zhang *et al* 2018 isolated four new tetramic acids, cladosins H−K, and a related known compound, cladodionen from the culture of the Mariana Trench (depth 6562 m) sediment-derived fungus *Cladosporium sphaerospermum* L3P3 treated with the histone deacetylase inhibitor SAHA (suberanilohydroxamic acid) [26]. Cladosins H and I are inseparable mixture of isomers with the ratio of 5:3 (1a:1b and 2a:2b) and have the same molecular formula of $C_{20}H_{26}N_2O_4$. Cladosins J and K are inseparable mixture with the ratio of 5:3 and have the same molecular formula of $C_{25}H_{29}N_3O_3$ (figure. 11). Compounds exist as equilibrium E/Z mixtures and were the first cases of tetramic acids containing aniline moieties [26]. Cladosins I-K show cytotoxicity at numerous levels against the K562 and HL-60 cell lines whereas, cladosins H was inactive (IC_{50} > 10 µM). Cladosins I, with the 8S configuration, shows less activity than cladosins I, with the 8R configuration, indicating the absolute configuration of C-8 was important for cytotoxicity and the aniline moiety is essential for enhancing cytotoxicity [26].

Sidra Kaleem *et al*. 2020 have conducted research on bioactive metabolites from the Mariana trench sediment-derived fungus *penicillium* sp. SY2107. They isolated the total of 16 compounds from the hadal fungus SY2107 collected at a depth of 11000 m of Mariana trench [22]. The structure of the new compound was elucidated one compound as new meroterpenoid, named andrastone C and others as known compounds: andrastone B (16-*epi*-citreohybriddione) A, (*Z*)-*N*-(4-hydroxystyryl) formamide, pyripyropene A, fumiquinazoline C, spirotryprostatin C, fumiquinazoline J, pseurotin A, penicilliumin B, (–)-viridin, monascusone A, aspergillumarin A, 1,2-seco-trypacidin, di-Me 2,3'-dimethylosoate, 2*S*-(2-hydroxypropanamido) benzamide, and bisdethiobis (methylthio) gliotoxin [22].

Andrastone C is monoclinic crystals and molecular formula is $C_{28}H_{36}O_8$ (figure. 12). Andrastone B is a meroterpenoid only just isolated from a deep-sea-derived fungus *Penicillium allii-sativi* and recorded its crystal structure for the first time. [22] The study carried out by Kaleem *et al*. 2020 revealed that andrastones C, andrastone B (16-*epi*-citreohybriddione) A, (*Z*)-*N*-(4-hydroxystyryl) formamide, pyripyropene A, fumiquinazoline C, spirotryprostatin C, fumiquinazoline J, pseurotin A, penicilliumin B, (–)-viridin, monascusone A and aspergillumarin A, had moderate antimicrobial activities against MRSA, *E. coli*, and *C. albicans*. On the other hand, 1,2-seco-trypacidin, di-Me 2,3'-dimethylosoate, 2*S*-(2-hydroxypropanamido) benzamide, and bisdethiobis (methylthio) gliotoxin only displayed moderate antibacterial activities against MRSA and *E. coli* [22].

Yi *et al* 2020 discovered new streptothiazolidine A, streptodiketopiperazines A and B, and (*S*)-1-(3ethylphenyl)-1,2-ethanediol, together with eight known compounds, identified as (*R*)-1-(3-ethylphenyl)1,2-ethanediol, orthocetamol, *N*-salicyloyl-2-aminopropan-1,3-diol, *N*-[2-hydroxy1-(hydroxymethyl) ethyl]-2-methoxybenzamide, salicylamide, 4-hydroxymethyl benzoate, 1, 9-dicarbomethoxyphenazine, and spoxazomicin C. These distinctive compounds were isolated from the actinomycete *Streptomyces* sp. SY1965 isolated from a Mariana Trench sediment collected at depth of 11,000 m. [21]

Streptothiazolidine A is a white amorphous powder and molecular formula is C17H25N3O4S. (figure. 13). Structurally, it is defined as a novel salicylamide analogue with a unique thiazolidine-contained side chain, called streptothiazomycin A, which was an analogue of spoxazomicins A and B, two rare antitrypanosomal alkaloids isolated from an endophytic actinomycete, *Streptosporangium oxazolinicum* K07-0460T. [28] It exhibits weak antifungal activity against *C. albicans* with an MIC value of 47 µg/mL [21].

Streptodiketopiperazines A and B is colorless monoclinic crystals and their molecular formula are $C_{13}H_{14}N_2O_2$ (figure. 14). They are racemic mixture of enantiomers. Accordingly, streptodiketopiperazines A is assigned as (S)-enantiomer and streptodiketopiperazines B is assigned as (R)-enantiomer [21].

They are structurally elucidated as two new diketopiperazine derivatives, similar to (3*Z*,6*S*)-3-ethylidene-1-methyl-6-(phenylmethyl)-2,5-piperazinedione, an A-factor mimic that restores antibiotic biosynthesis and morphogenesis in *Streptomyces globisporus* 1912-B2 and *Streptomyces griseus* 1439 [28]. Both exhibit weak antifungal activity against *C. albicans* with an MIC value of 42 µg/mL. [21] (*S*)-1-(3ethylphenyl)-1,2-ethanediol is also a racemic mixture and is a new phenylethanediol, corresponding to a molecular formula, $C_{10}H_{14}O_2$ [21] (figure. 15) The structure of new pyrrole alkaloids, named new subtipyrroline A-C were elucidated from *Bacillus subtilis* SY2101 isolated from a sediment sample collected from the Mariana Trench at a depth of 11,000 m by Qin *et al* 2020. [23] Subtipyrroline A is yellow orthorhombic crystals and the molecular formula is $C_{11}H_{11}N_3O_2$ [23] (figure. 16) The molecular formula subtipyrroline B and C are $C_{15}H_{17}N_3O_4$ and $C_{22}H_{22}N_4O_4$ (figure. 17-18). The subtipyrrolines A-C have a distinctive pyrrole-pyrrole-dihydropyridine tricyclic skeleton. Subtipyrrolines A and C showed weak activities against human glioma cell lines U251 (IC_{50}: 36.3 mM) and U87MG (IC_{50}: 26.1 mM), respectively. Subtipyrrolines A-C had weak antimicrobial activities with MIC values of 45-46 mg/mL against *E. coli* and 34-37 mg/mL against *C. albicans* [23].

Lu *et al* 2021 isolated 4 polyketides including three new compounds, phomanones A-C, and a known compound, 2-hydroxymethyl-3-methylcyclopent-2-enone from *Phoma* sp. HDN16-618, a fungus derived from a sea water sample collected from Mariana Trench [30].

Phomanone A is a colorless oil and the molecular formula is $C_8H_{12}O_2S$ [30]. (figure. 19) It is an unusual sulfur-containing cyclopentenone. Phomanone B is also a colorless oil and the molecular formula is $C_9H_{12}O_5$. [30] (figure. 20) The molecular formula of Phomanone C is $C_{10}H_{14}O_5$ (figure. 21). These compounds showed no significant cytotoxicities against the HL-60, K562, BEL-7402, HCT-116, A549, Hela, L-02, MGC-803, HO8910, SH-SY5Y, PC-3, U87, and MDA-MB-231 cell lines (IC_{50} > 30 µM). [30]

Research scheme for the study of secondary metabolites from the marine microorganisms isolated from Mariana Trench sediments

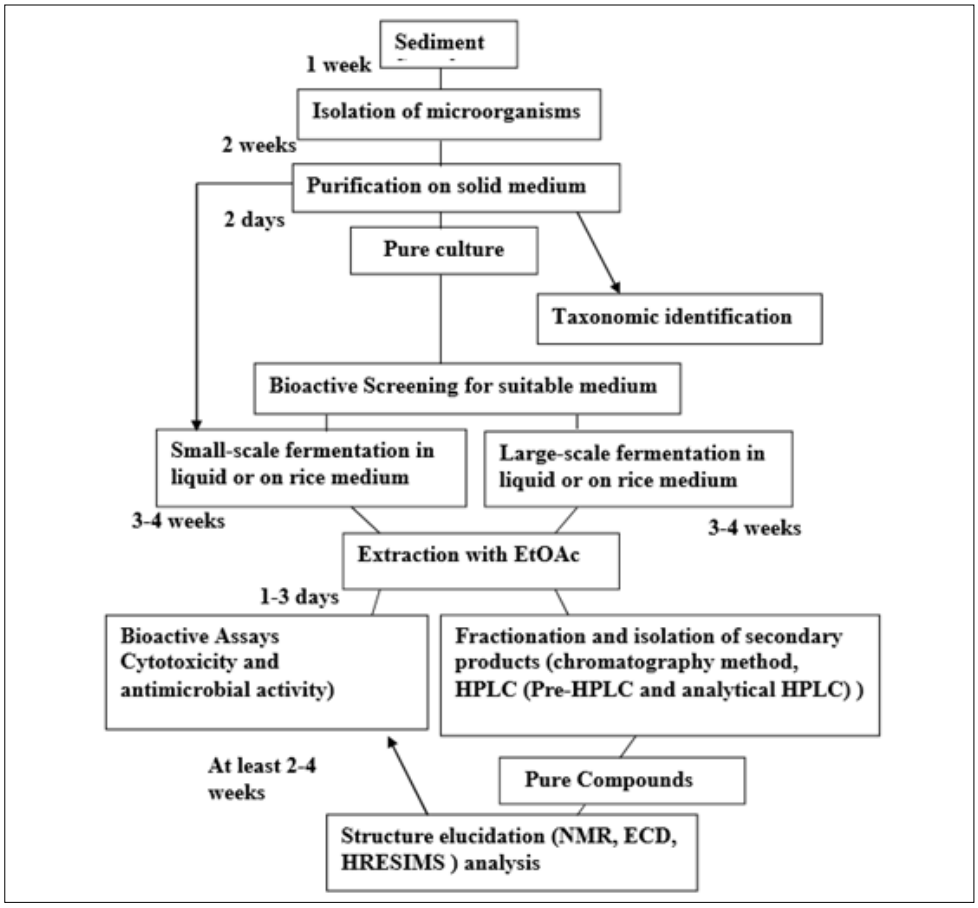

Fig 1

Conclusions

To my best knowledge, there have been only a few studies about secondary metabolites isolated from hadal sediment in Mariana trench. The reason is because it is so difficult to go and explore there due to the intense pressures in the deep ocean. However, this highly hydrostatic pressures and higher abundance of organic matter make it microbial communities distinct from those at shallower depths. Although the references about secondary metabolites isolated from Mariana trench sediments are meagre, the twenty-nine number of new novel metabolites including fourteen new phenazine compounds, four new tetramic acids, one new meroterpenoid, three new pyrrole alkaloids, one new novel salicylamide analogue, two new diketopiperazine derivatives, one new phenylethanediol and three new polyketides have been explored by the researchers. Therefore, it can be assumed that Mariana trench can bestow numerous new novel compounds for drug discovery. In the modern days, the investigations of microbial communities in hadal sediment have been emphasized due to the rapid technical progress in deep-sea sampling. At last but not least, this review suggests for the researchers to consider the microorganisms in Mariana trench's sediment as a source of unexplored and new chemical diversity for drug discovery and provides the future investigations about secondary metabolites isolated from microorganisms in deep-sea sediments of Mariana trench.

Conflict of interest

There is no conflict of interest to declare.

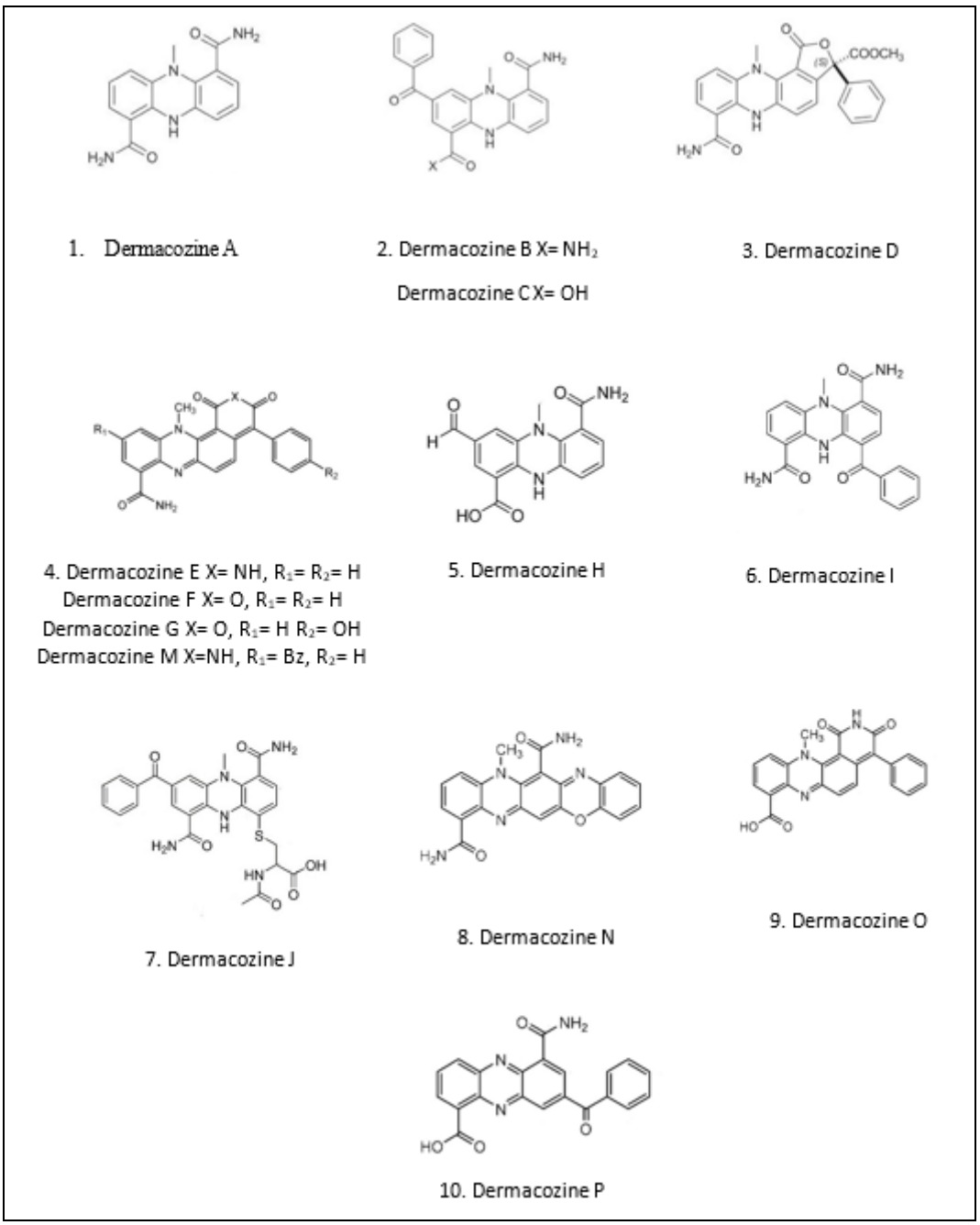

Fig 2

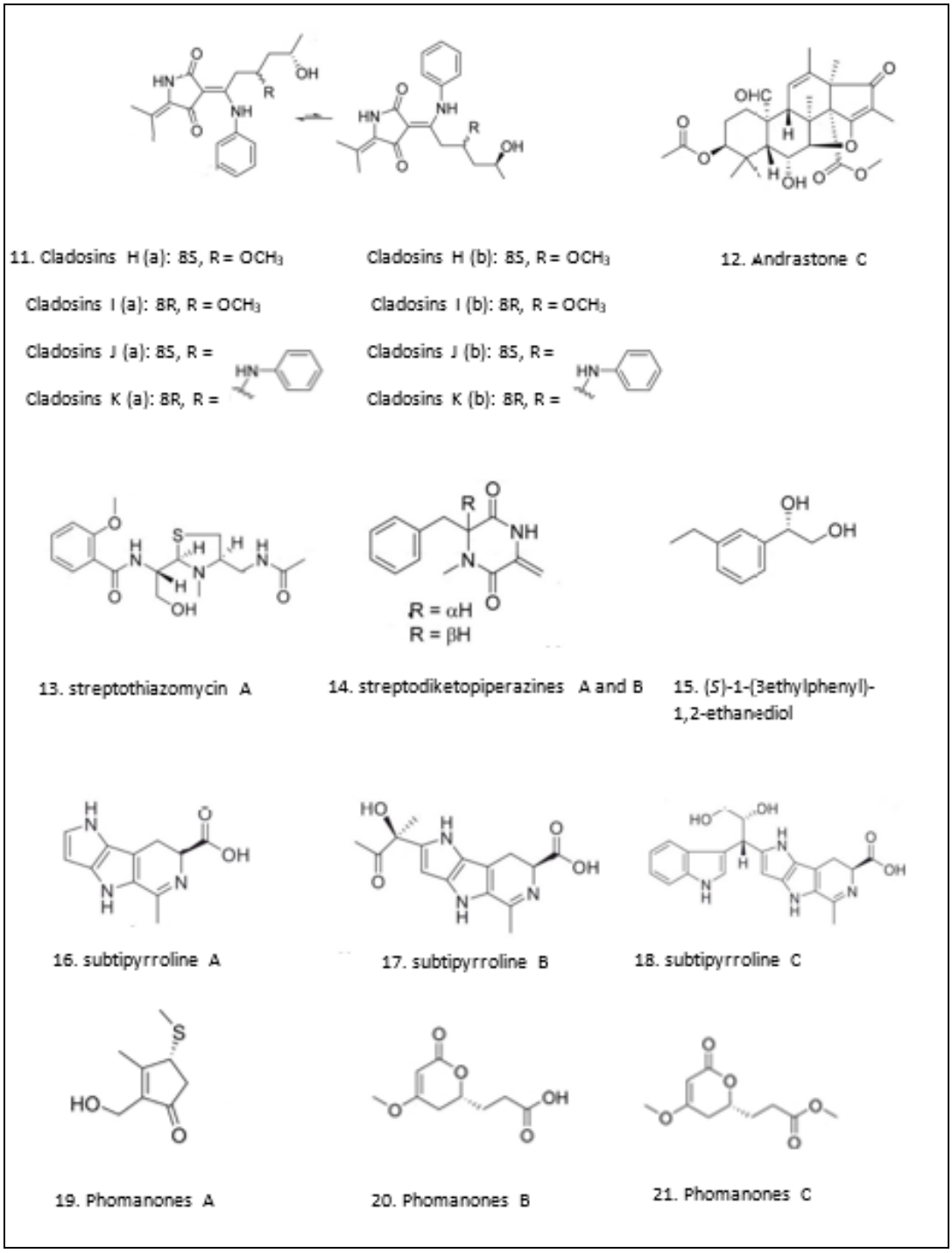

Fig 3

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