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REVIEW ARTICLE

Are There Any Other Compounds Isolated From *Dermacoccus* spp at All?

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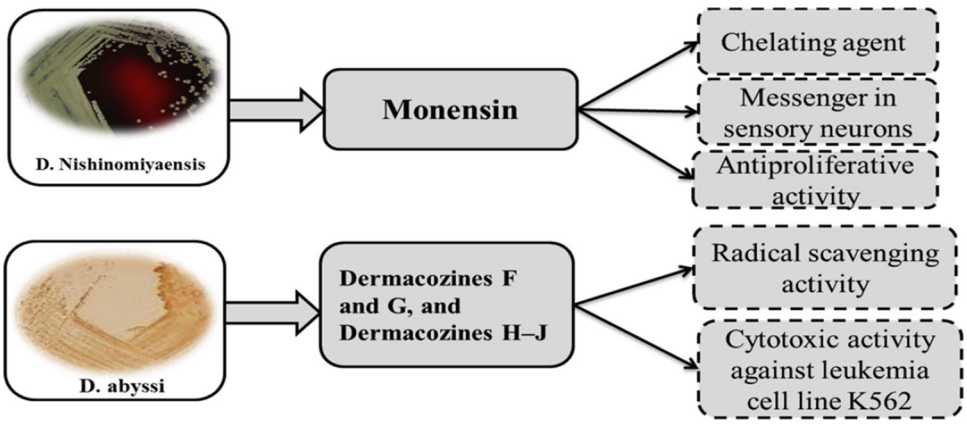
Abstract Microbial-derived natural products have functional and structural diversity and complexity. For several decades, they have provided the basic foundation for most drugs available to modern medicine. Microbial-derived natural products have wide-ranging applications, especially as chemotherapeutics for various diseases and disorders. By exploring distinct microorganisms in different environments, small novel bioactive molecules with unique functionalities and biological or biomedical significance can be identified. Aquatic environments, such as oceans or seas, are considered to be sources of abundant novel bioactive compounds. Studies on marine microorganisms have revealed that several bioactive compounds extracted from marine algae and invertebrates are eventually generated by their associated bacteria. These findings have prompted intense research interest in discovering novel compounds from marine microorganisms. Natural products derived from *Dermacoccus* exhibit antibacterial, antitumor, antifungal, antioxidant, antiviral, antiparasitic, and eventually immunosuppressive bioactivities. In this review, we discussed the diversity of secondary metabolites generated by genus *Dermacoccus* with respect to their chemical structure, biological activity, and origin. This brief review highlights and showcases the pivotal importance of *Dermacoccus*-derived natural products and sheds light on the potential venues of discovery of new bioactive compounds from marine microorganisms.

Graphical Abstract



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Introduction

Marine microbes have a special significance to everyday life. There is a possibility that marine microorganisms could be the closest relatives of initial life forms, as life is believed to have started in the oceans. They are capable of carrying out numerous stages in biochemical sequences that are impossible for other organisms as a result of their metabolic abilities and diversities, and they are also employed for several biochemical uses, such as the production of industrial goods [63, 65, 92]. In specific members of the order Actinomycetales, marine microbes are excellent sources of new metabolites with potential pharmaceutical application [7, 24]. More than 140 actinomycete genera have been reported, and a few of them have been identified to be major sources of known essential compounds [7, 42, 77]. Furthermore, other actinomycetes like *Saccharopolyspora*, *Amycolatopsis*, *Micromonospora,* and *Actinoplanes* also generate small bioactive metabolic molecules. Actinomycete strains may be present in different habitats: Many are usually present in terrestrial soils, although others have also been isolated from marine sediments and sponges [23, 75]. Actinomycetes provide the foundation for the synthesis of useful natural products with biological, biomedical, and pharmaceutical importance. For a long time, actinomycetes have been the most popular and known for their application as antibiotics. Moreover, their previously documented use as an antifungal agent is responsible for their popularity with antibiotic research today. Actinomycetes include a substantially large group of species with a wide range of applications in food, biomedical, and pharmaceutical industries [98].

In 1995, Stackebrandt et al. [94] suggested that the monospecific genus *Dermacoccus* should be classified under actinomycetes [94]. Based on 16S rDNA gene sequence comparison, the genus *Dermacoccus* is classified under the Dermacoccaceae family [96], which includes other genera such as *Demetria* [33] and *Kytococcus* [94]. Previous studies have identified and characterized several species of this family, such as *D. nishinomiyaensis*, *D. abyssi*, *D. barathri*, *D. sedentarius*, and *D. profundi* [72, 94].

One member of this group, *D. Nishinomiyaensis*, is often distinguished by its terrestrial environmental contexts like soil, salt, and partially preserved meat items [15, 19, 69, 89]. Furthermore, within Chinese residential homes, *D. profundi* has been traced [22], and *D. barathri* has been detected from soil and water [89].

D. Nishinomiyaensis was previously known as *Micrococcus nishinomiyaensis*. More than 100 years ago, the genus *Micrococcus* was first reported and initially characterized, and since then the initial description has been revised multiple times. It has been revealed that *D. Nishinomiyaensis*, which phenotypically belongs to the large group of Gram-positive and catalase-positive cocci, is phylogenetically considered as a member of the actinomycete group [95]. Several features that characterize this genus include the spherically shaped cells (diameter range from 0.9 to 1.6 pm) and their occurrence in pairs, tetrads, or irregular clusters of tetrads. Their colonies grow up to 2 mm in diameter, and are circular in shape, slightly convex with glistening smooth surfaces, and bright orange in color. *D. nishinomiyaensis* can grow well in up to 5% NaCI, but no growth occurs in the presence of 7% NaCl. Optimum growth temperature was reported to be in the range of 25 to 37 °C [94].

D. abyssi is detailed as non-acid-alcohol-fast, non-motile actinomycete. Its cells are coccoid-shaped with diameters between 0.8 and 1.5 µm, appearing in uneven groups. Smooth, shiny colonies that are colored pale-yellow to cream, which are circular, entire, or convex, are created on agar from glucose yeast extract at 28 °C for 5 days. *D. abyssi* develops swiftly on tryptic soy agar, although not as well on inorganic nitrogen agar. Development takes place from 10 to 37 °C, with optimum development at about 28 °C. Degradation of hypoxanthine, cellulose, uric acid, starch, and casein take place. Development happens with the availability of 7.5% NaCl. Glucose yeast extract broth promotes satisfactory development of *D. abyssi* at 40 MPa [72]. In the present work, we discuss the medical applications of secondary metabolites isolated from *D. nishinomiyaensis* and *D. abyssi*, as well as highlight their molecular mode of activities and potential medical applications.

Dermacoccus spp Role in Bacterial Community

Many reports have established the function of *Dermacoccus* within the bacterial community. Phylogenetic evaluations of the culturable proportion of the bacterial community separated from the marine sponge *Erylus deficiens* disclosed the availability of *Dermacoccus*. Numerous *Erylus* isolates were seen to show antibacterial and high antifungal bioactivities against pathogenic and environmental strains. Polyketide synthases (PKS) and Novel non-ribosomal peptide synthetase (NRPS) genes may also have relation to a few *Erylus* isolates. As a result, the raised bioactivity levels and the fact that there could be some related genes hint that *Erylus deficiens* bacteria may be the origin of new marine bioactive mixtures [30]. Scrutiny of gastrointestinal GI tract communities of *Panaque nigrolineatus* produced by anaerobic microcrystalline cellulose enhancement cultures through 16S rRNA gene examination showed phylotypes having a common high sequence likeness to recognized cellulolytic

bacteria such as *Dermacoccus nishinomiyaensis, Clostridium xylanolyticum, Cellulomonas chitinilytica, Bacteroides xylanolyticus, Eubacterium contortum, and Aeromonas spp.* For this reason, the *P. nigrolineatus* GI tract is a better environment for cellulose degrading, and these communities might have to deal with the availability of assimilable carbon in the case of difficult dietary conditions [104]. *Paenibacillus* sp., *Leifsonia* sp. and *Bacillus* sp. had the greatest numbers in the rhizosphere linked to 'Belgisch Rood'(BR) willow clone, at 22.04, 20.81, and 21.27%, respectively, for the individual strains. The other proportion of the isolated BR-related rhizosphere bacteria was made up of *Streptomyces* sp. (13.29%), *Dermacoccus* sp. (7.97%), *Luteibacter* sp. (7.97%), and *Caulobacter* sp [106]. Wittebolle et al. [107] outlined that the performance of a bacterial community with greater diversity has greater resistance to stress from the environment than that of a bacterial community with reduced diversity. Being aware of this, endophytic bacterial diversity seen in 'Tora' (TO) clone could bring about improved performance for the endophytic TO-related bacterial community with the current metal stress, which could assist improved maturity and growth of the host plant [107]. Analysis of the upper buttock showed a strong gender effect with males displaying relatively high proportions of *Corynebacterium*, *Dermacoccus*, *Streptococcus*, and *Finegoldia*, while females exhibited greater levels of *Lactobacillus*, *Propionibacterium*, *Staphylococcus*, and *Enhydrobacter* [110]. Bacterial colonization on human skin begins at birth and carries on all through the early years of life. The microbial communities later stabilize and assist in the formation of cutaneous homeostasis and control of inherent human responses [9]. The brief or long-term availability of these microbes on the skin is reliant on the topographical areas of the body which have varying particular conditions (such as pH, moisture, and sebum content), factors specific to the host (such as age and gender), and environmental aspects particular to the individual (such as geographical location, occupation, lifestyle, use of antibiotics, use of cosmetics, and soaps) [32]. Remarkably, the microbiome of the deeper stratum corneum layers remarkably has an important function in the skin's microbial recolonization procedure following injury. Additionally, microbiome dynamics of the human epidermis after disruption of the skin barrier displayed great interpersonal variation, and significant differences due to gender [110]. Pang et al. [68] reported that three out of four bacterial isolates taken from a reverse osmosis (RO) membrane treating potable water (*Dermacoccus* RO12, *Microbacterium* RO18, and *Rhodopseudomonas* RO3) were reported as not displaying swimming motility, which suggested that they could be conveyed to the surface of the membrane by means of other structures including convective permeate flow [68].

Dermacoccus Nishinomiyaensis

D. nishinomiyaensis has demonstrated the capability to produce monensins A and B using a soya bean medium [80], within flat-bottomed flasks of volume 500 mL at 34 °C for 10 days on a rotary shaker (162 rpm) with the origin of carbon being lactose or fructose [79]. Monensins are oligomers with C2–C4 units comprising acetate, propionate, and butyrate [18]. The salts from this group of compounds exhibit significant medical importance. For instance, the compound monensin sodium is a known polyether ionophore antibiotic that can control and counteract specific viral infections [49].

Biosynthetic Trajectory of Monensin A

Monensin, which has several homologues such as monensin A, B, and C, was isolated for the first time in 1967. Monensin sodium salt has been biosynthesized in the culture of *S. cinnamonensis* [18, 48, 86]. Monensin A, which is oxidized to the corresponding polyepoxide, is produced in a classic polyketide pathway from seven propionate, one butyrate, and five acetate units [8]. According to Bhatt et al. [5], activation of oxidative cyclization does not precede production of the full-length chain, while a linear enzyme-bound (E,E,E)-triene known as "premonensin" is the original PKS product [5]. The tri-epoxide 3 is produced as a result of the catalysis of three stereospecific epoxidations by the flavin-dependent epoxidase MonCI and is subsequently subjected to a cascade of ring opening/closing. The unusual epoxide hydrolases MonBI and MonBII then act together to catalyze this cascade and generate the supposed protein-bound intermediate dehydroxydemethylmonensin [61]. The following stages involve hydroxylation at C-26 with cytochrome P450 hydroxylase MonD acting as catalyst and hydroxy group O-methylation at C-3 with the catalyst methyltransferase MonE [37]. In Fig. 1, methylation is demonstrated to take place following hydroxylation, although in actuality no regulation has been enforced concerning the sequence of these procedures. The generation of mature monensins A and B from MonACPX, with the irregular thioesterase MonCII functioning as a catalyst, comprises the final biosynthesis phase [40].

Clinical Applications of Monensin

In the current large-scale industries, exposure to heavy metals, such as lead, presents a major health problem faced by both developed and developing countries [25, 31, 67, 73]. Lead exposure has various negative effects on the

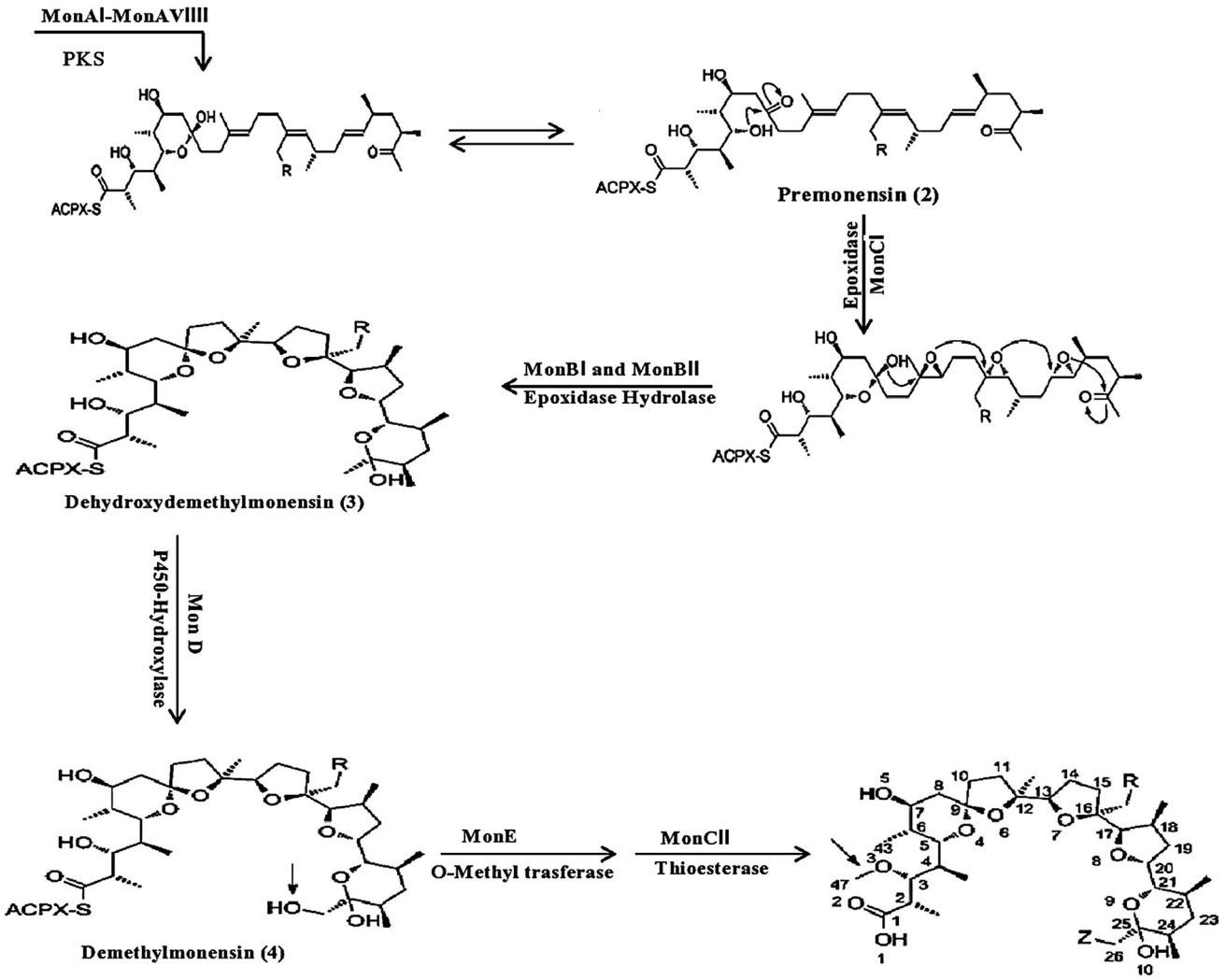

Fig. 1 The suggested model through which monensin can be biosynthesized in the case of *Streptomyces cinnamonensis* (Reproduced with permission of author [39])

function of different organs, such as the spleen, liver, kidneys, and brain [25]. Notably, the nervous system is the most sensitive to lead-induced toxicity [13, 16, 64, 90]. Furthermore, lead was reported to destroy the function of hematopoietic system cells [78]. Despite its cellular toxicity, the biochemical activity of this toxic metal was shown to resemble that of other divalent metal ions, such as calcium [51]. Intoxicated male mice exposed to lead salts showed significant accumulation of lead in all studied organs compared with the untreated control animals [41]. The results from this study revealed that the bio-distribution of lead occurred in the following order: kidneys > spleen > liver > brain. Interestingly, the treatment of the lead-intoxicated animals with tetraethylammonium salts of monensin significantly mitigated the accumulation of the toxic metal, compared to the toxic control animals. The previously observed effect varied from 38% (for kidneys) to 52% (for brain) compared to the toxic control group (lead). Therefore, monensin is considered to be a potential chelating agent for the treatment of lead poisoning [41]. Through monensin treatment, the expression of Penk mRNA was down-regulated, whereas that of *Ceacam10* was increased without affecting the *Gapdh* gene in DRG neurons obtained from wild-type mice. These results

indicated that monensin could serve as a second messenger in sensory neurons for the regulation of gene expression [62]. It has been reported that monensin exhibits antiviral, antifungal, antiparasitic, antimalarial, anti-inflammatory, and tumor cell cytotoxic activity [10, 35, 45, 81]. Recently, the anti-neoplastic activity of polyether ionophores was substantially supported by the finding that these compounds may be able to kill cancer stem cells and mitigate the growth of breast cancer, and metastasis in mice [34, 109]. Such effects partly resulted from the alteration of the intracellular pH by ionophores [55]. The tumor growth has been suppressed in the APC+/Min mice after the treatment by monensin. While the average number of tumors has remained unchanged in the treated animals, the size of neoplastic lesions was reduced. These findings indicated that monensin plays a role in tumor progression inhibition instead of the tumor initiation process [100].

Several studies have demonstrated that monensins exhibit antiproliferative activity against several cancer cell lines and their models, such as human colon cancer, lymphoma, and myeloma. Specifically, it was revealed that monensin induces G1 and/or G2-M arrest during the cell cycle of these cells. The potent cytotoxic effect of this ionophore and its crucial function in counteracting the multi-drug resistance of cancer cells has been also demonstrated previously. Only four compounds, including monensin, of 4910 tested compounds show a specific inhibition on the proliferation and growth of prostate cancer cells at a small concentration scale such as nanomolar concentrations [14, 21, 44, 52, 53, 66, 105].

The major mechanism of monensin as a cation carrier is the electrically silent exchange of sodium (or potassium) cations for protons across the membrane. Monensin can perform non-electrogenic exchange of potassium (sodium) ions for protons and serve as electrogenic potassium ion carriers similar to valinomycin [81, 105]. The functional activity observed on artificial membranes and mitochondria can explain the function of monensin and its derivatives in living systems related to ionophorous properties and the action on the oxidative phosphorylation. This work is particularly important in the study of the antitumor activity of monensin and similar polyether ionophores, especially as apoptotic cell death is frequently associated with the perturbation of mitochondria through the induction of oxidative stress, activation of pro-apoptotic proteins localized in the mitochondria, and release of cytochrome C. Thus, the swelling of the mitochondria can be assumed to trigger the process of mitochondrial perturbation [2].

The synergistic effect of monensin with EGFR inhibitors and oxaliplatin has been demonstrated through the inhibition of cell proliferation and induced apoptosis of ovarian cancer cells. Xenograft studies showed that tumor growth was effectively inhibited by repressing cell proliferation, by targeting EGFR signaling. Therefore, monensin could be used as a therapeutic agent for ovarian cancer treatment, although future investigations are required [20]. Moreover, an interaction between monensin and silybin considerably reduced the cytotoxicity within cell line cultures of HepG2, LMH, and L6. These findings confirmed that the action of monensin mainly focused on the metabolism of HepG2 and LMH cells, leading to their severe impairment [17]. However, the disintegration of the cell membrane in the rat myoblasts covered by monensin appeared as a prevalent mechanism of cytotoxicity [83, 84]. Therefore, these results might represent a useful

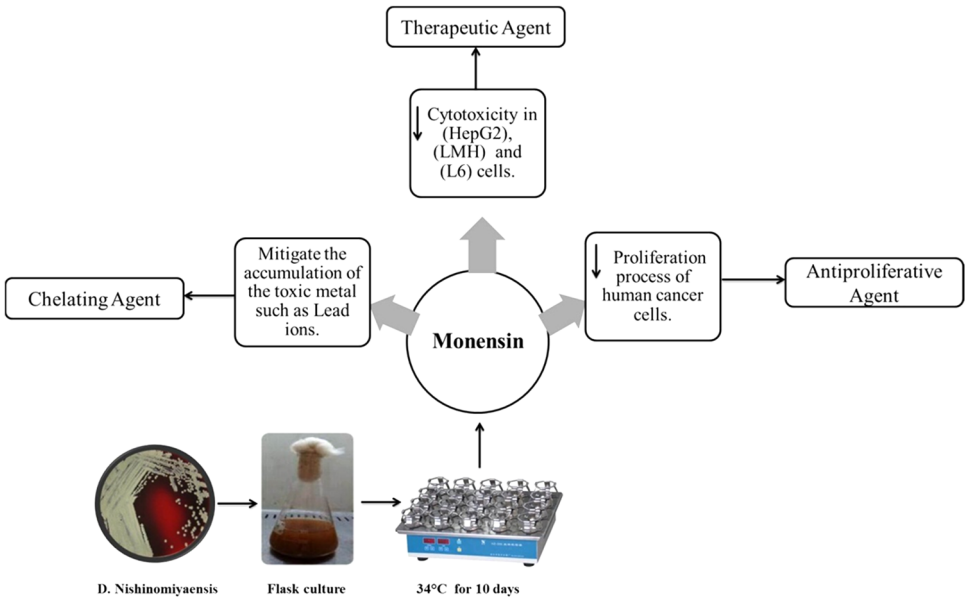

Fig. 2 Clinical applications of monensin

approach for the applicability of monensin in human therapy [17]. The clinical applications of monensin are summarized in Fig. 2.

Due to it exhibiting such high biological activity, monensin is considered as an attractive molecule for biomedical and biological investigations. As a result, several chemical modifications have been performed on this compound to improve its bioactivity and its bioavailability. Depending on the nature and site of modification, the resulting derivatives may differ in their activities, toxicities, and selectivity of cation complexity compared to that of the parental compound [53]. Various modifications on the COOH group of monensin have been performed frequently to generate a series of secondary amide and ester derivatives that can exhibit biological activity against various Gram-positive bacterial species; for instance, these effects have been demonstrated against strains obtained from hospitals, such as methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* strains [54]. This resistance suggested the need for chemically improved versions of monensin that can exhibit higher efficacy. Indeed, new tertiary amide derivatives of polyether ionophore monensin A were synthesized, and their anti-neoplastic activity against human cancer cell lines was studied. Monensin A showed very high activity ($IC_{50} = 0.09$ μM) and selectivity (SI = 232) toward human biphenotypic myelomonocytic leukemia cell line (MV4-11). Thus, the generated derivatives of monensin demonstrated remarkable anti-neoplastic activity, high selectivity, and the ability to bypass the drug resistance of some cancer cell lines [39].

Dermacoccus Abyssi

Two strains of *D. abyssi* (MT1.1 and MT1.2) have been isolated from Mariana sediments at a depth of approximately 10 898 m. The MT1.1 *D. abyssi* strain was developed in baffled shake flasks of volume 250 mL, comprising 70 mL yeast extract-malt extract broth [91] with the availability of HP20 resin over 7 days at a temperature of 28 C, following first-phase seeding in 10 mL glucose yeast extract [29]. The MT 1.2 *D. abyssi* strain was grown in a multifarious medium within 500-mL Erlenmeyer flasks comprising one baffle due to its intense foaming features which appeared in stirred-tank fermenters with aeration [1]. The process of fermentation using complex media resulted in the production of seven new oxidized and reduced phenazine-type pigments, dermacozines A–G (1–7), as well as the well-known phenazine-1-carboxylic acid (PCA) (8) and phenazine-1,6-dicarboxylic acid (9) [1] (Fig. 3).

Biogenetic Pathway of Dermacozines

Like the majority of natural phenazine products, dermacozines are thought to be originated through the shikimic acid pathway, as highlighted in Fig. 4, with chorismic acid comprising the most likely branch point intermediate. Shikimic acid is changed to chorismic acid within acknowledged alterations which comprise elements of the aromatic amino acid biosynthetic trajectory [50, 58, 76, 88]. The conversion from chorismic acid into the phenazine precursors is catalyzed by a sequence of phenazine synthesis-particular enzyme-managed stages to provide trans-2,3-dihydro-3-hydroxyanthranilic acid (DHHA) [60, 70, 71]. Two DHHA molecules can condense themselves to create phenazine-1,6- dicarboxylic acid (9) [6, 27, 57, 60, 101]. An optional trajectory would progress through aminodehyroquinic acid to 5-amino-5-deoxyshikimic acid, which during self-condensation, dehydration, and oxidation, could result in the creation of phenazine-1,6-dicarboxylic acid or its decreased state, which comprise the key precursors for additionally intricate phenazine metabolites [46, 101].

At some point, phenazine-1,6-dicarboxylic acid would experience N-methylation and single or double amide bond creation, producing a dermacozine A-type biogenetic intermediate [11]. This would pair with a C6–C1 or C6–C2 building block to produce dermacozine B/C compounds or dermacozine D-G congeners. Within this setting, it is remarkable to observe that phenylacetic acid as well as its amide was traced within the culture medium [1]. Ghanta et al. [26] have reported that Dermacozines A, B, and C were synthesized from a commercially available methyl 2-bromo-3-nitrobenzoate and methyl 3-amino-2-chlorobenzoate. The key carbon–carbon and carbon–nitrogen bond-forming reactions include inter- and intramolecular palladium Pd (0)-catalyzed N-arylations and regioselective Friedel–Crafts benzoylation, respectively. Nitrile group, which is considered as a masked carboxylic group, has been used to functionalize two carboxylic acids to produce Dermacozine C [26].

Biological Activities of Phenazines

Phenazines are extracted as secondary metabolite molecules from *Streptomyces, Pseudomonas,* and other bacterial strains from diverse habitats including soil and marine. Phenazines have antimicrobial, antiparasitic, and anti-neoplastic activities [12, 50, 56, 59, 82]. PCA, generated by the fluorescent pseudomonads, comprised a significant component of the new antifungal pesticide Shenqinmycin [108], which is described as a potent and broad-spectrum antifungal metabolic molecule [36, 38, 85, 99]. PCA,

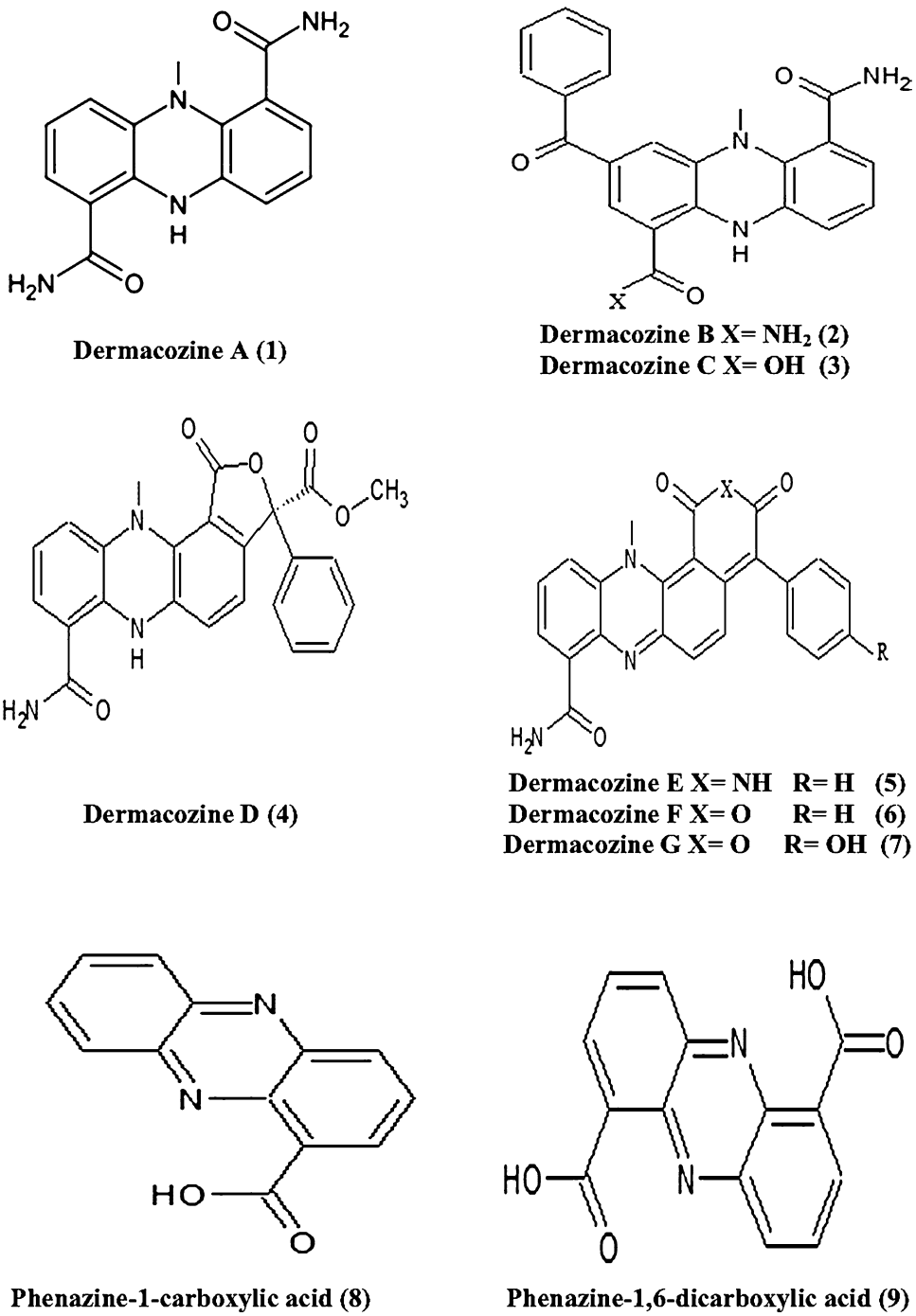

Fig. 3 Chemical structure of dermacozines A–G (1–7), phenazine-1-carboxylic acid (8), and phenazine-1,6-dicarboxylic acid (9)

known as tubermycin B with potent antibiotic activity against *Mycobacterium tuberculosis*, is one of the simplest molecules of the phenazine group [50]. Moreover, PCA has been shown to facilitate bacterial biofilm formation via ferrous iron sequestering. While it has become clear that iron is required for the growth of organisms, it is well known that the biofilm formation required an amount of iron in excess of this need [3, 4, 74, 87, 93]. Thus, the PCA present in infected cells can alter the kinetics of the redox equilibrium between Fe(III) and Fe(II), and thereby make iron ions relatively more bioavailable [103]. The highest activity of 4 μg/mL by PCA has been recorded against *Trichophyton rubrum*, a human pathogen that causes athlete's foot, jock itch, ringworm, and fingernail fungal infections, followed by the potency of PCA against *Candida albicans* and *C. tropicalis* [28]. Interestingly, 5-methyl phenazine-1-carboxylic acid betaine (MPCAB) has a potent specific cytotoxicity toward various human cell lines, including lung and breast cancer cell lines, in a dose-dependent manner with IC_{50} values of 488.7 ± 2.52

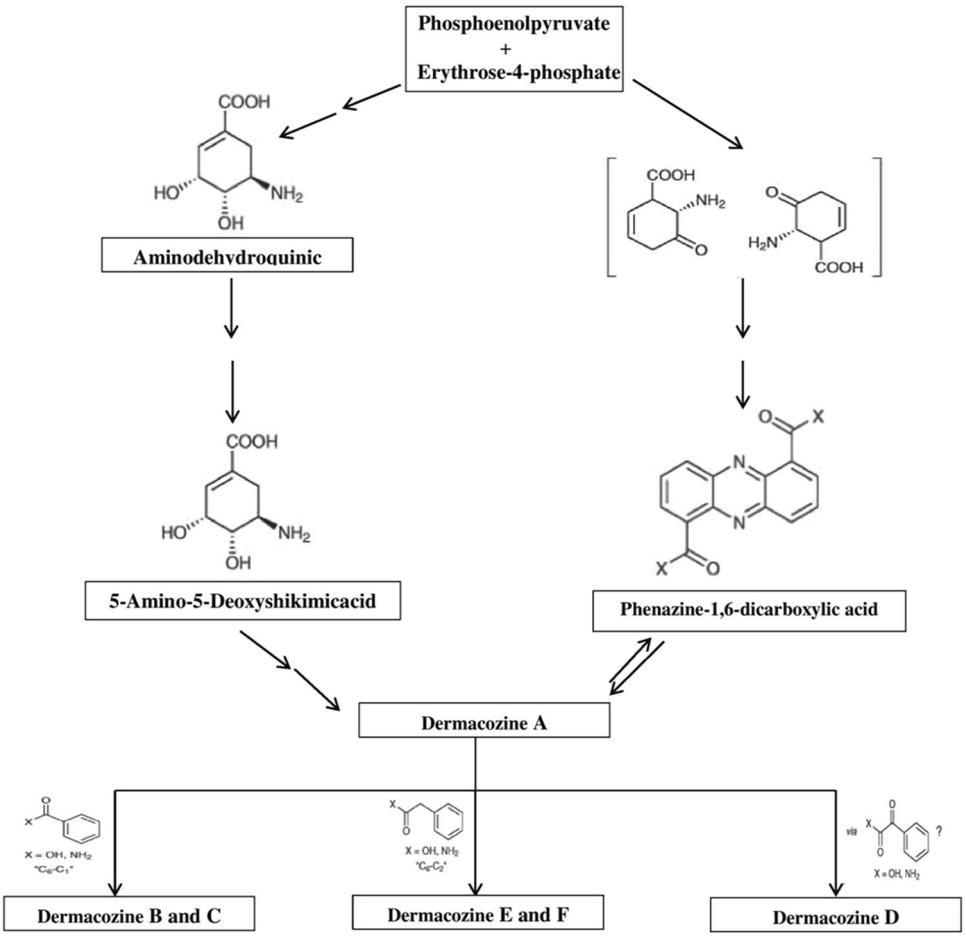

Fig. 4 Proposed biogenetic pathway for the dermacozines (Reproduced with permission of author [76])

and 458.6 ± 2.48 nM, respectively [43]. Furthermore, the cytotoxicity of MPCAB may stem from several molecular effects, including the inhibition of cell viability, inhibition of DNA synthesis, induction of G1 cell cycle arrest, and induction of apoptosis in cancer cells [47, 97]. Docking and interaction studies further solidified and confirmed the binding potential of MPCAB with antiapoptotic proteins, such as Bcl-2, Bcl-xL, and Bcl-w proteins. These results significantly suggest that treatment with MPCAB induced apoptotic cell death in cancer cells through the intrinsic mitochondrial pathway via the activation pro-apoptotic proteases, particularly caspase-3, and the down-regulation of antiapoptotic Bcl-2 protein [43].

As discussed beforehand, the dermacozines are phenazine alkaloids, and the phenazines are naturally created by cells which have ceased dividing and slowly metabolizing. There is no apparent role of phenazine metabolites in cell development, i.e., no significance as origins of energy or reserve materials of any sort. The absence of apparent phenazine metabolic roles has resulted in a number of theories on their physiological function in nature. The fact that phenazine-generating organisms endure longer in their natural settings as contrasted to non-phenazine-generating species has been illustrated [50]. Thus, it is feasible that the phenazines signify a bacterial protective element, resulting from their obvious antibiotic activity, which functions to safeguard the producing organism and its environment against alternative microbial rivals and microorganisms, and therefore enhances the living circumstances of the host organism [50]. Alternative acknowledged biological operations comprise antimalarial, antitumour, antiparasitic, and antioxidant. The likely mode of operation comprises the limitation or control of DNA (groove binding or intercalation), protein and RNA synthesis in addition to disturbance of metabolic procedures that necessitate energy [50].

Dermacozines F (6) and G (7) have a significant cytotoxic activity against chronic myeloid leukemia cell line K562 with IC_{50} values of 9 and 7 μM, respectively. Furthermore, the maximum radical scavenger activity was noted for dermacozine C (3), with an IC_{50} value of 8.4 μM [1].

Furthermore, the dermacozines H–J (Fig. 5) extracted from *D. abyssi* have demonstrated radical scavenging activity; the highest activity was observed for dermacozine H (1), with an IC_{50} value of 18.8 μM [102]. The efficacy of dermacozines A–G and PCA toward various diseases are shown in Fig. 6.

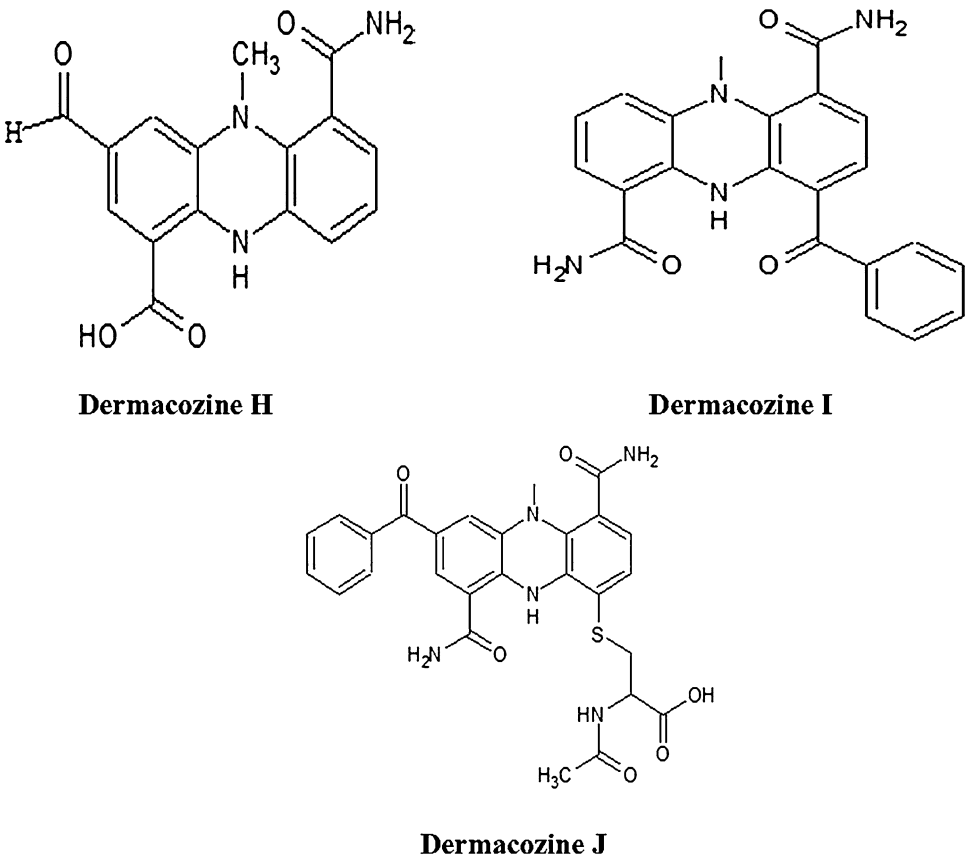

Fig. 5 Chemical structure of dermacozines H–J

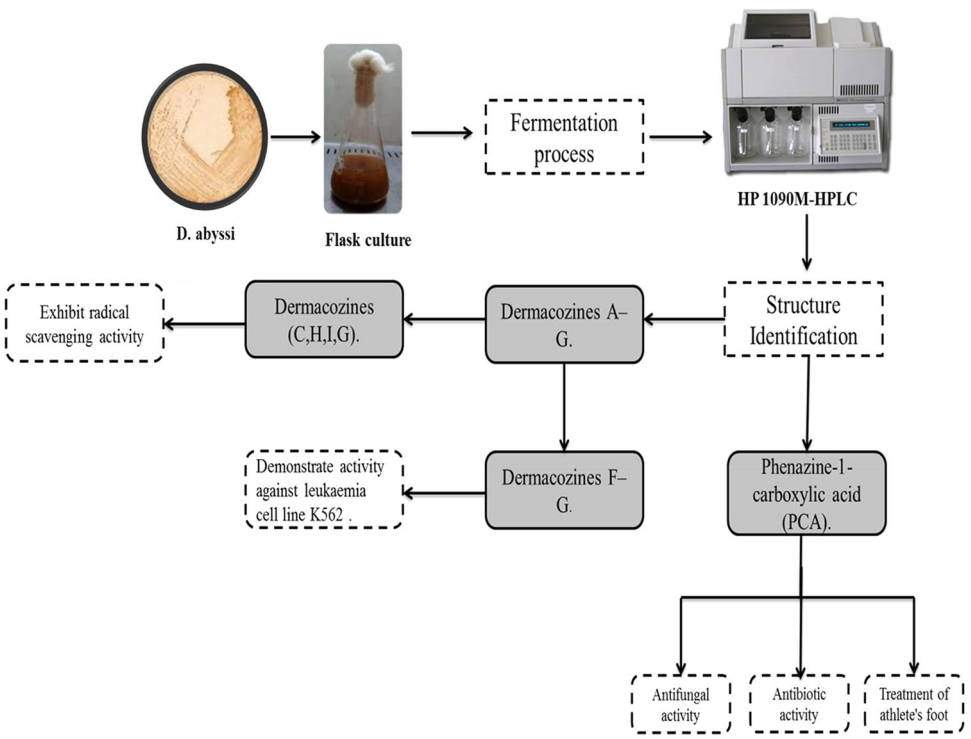

Fig. 6 The activity of Dermacozines A-G and phenazine-1-carboxylic acid in the prevention or treatment of various diseases

Conclusion and Future Prospects

Small, secondary metabolic molecules derived from microbes have become a wealthy source of compounds with unique chemical structures and broad biomedical functions. During microbial fermentation, numerous structurally diverse molecules are generated. These natural products have been shown to exhibit various biological activities, such as antibacterial, anticancer, antifungal, immunosuppressive, antioxidant, antiviral, antiparasitic, enzyme-inhibiting, and neuroprotective. Studying the original structures of parent bioactive molecules may prompt the development of unique candidates for novel and potent therapeutics. There is the fact that several secondary metabolic molecules with antibacterial activity led to the broad usage of these molecules and their derived compounds in the treatment of infectious diseases. A large number of bioactive compounds were originally isolated from the soil, which is an easily accessible environment. Current investigations study new strains from less accessible places, such as seas and oceans. The recent emergence of multi-drug resistant strains and the urgent need for improved tumor treatment support the efforts for a continuous study of novel natural bioactive metabolites. In summary, microbial organisms like bacteria represent a rich source of diverse and unique bioactive molecules with potent biological activity, and this area of research still needs to be investigated in the future.

In sum, we suggest that future research should focus on (i) investigating the cytotoxic effect of monensin in vivo; (ii) examining *D. abyssi*-derived PCA and phenazine-1,6-dicarboxylic acid as bioactive products against diverse types of diseases; (iii) investigating the optimal growth conditions for *D. abyssi* and *D. Nishinomiyaensis* to optimize the high-yield production of PCA and monensin; and (v) identifying and examining the novel compounds and enzymes from *D. profundi* or *D. barathri*, which could exhibit biotechnological properties for biomedical, pharmaceutical, and industrial applications.

Compliance with Ethical Standards

Conflict of interest The authors confirm that this article content has no conflict of interest.

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