Modulators of Mitochondrial Biology Derived from Marine Resources

Subjects: Biology

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Mitochondria are double-membrane organelles within eukaryotic cells that act as cellular power houses owing to their ability to efficiently generate the ATP required to sustain normal cell function. Also, they represent a “hub” for the regulation of a plethora of processes, including cellular homeostasis, metabolism, the defense against oxidative stress, and cell death. Mitochondrial dysfunctions are associated with a wide range of human diseases with complex pathologies, including metabolic diseases, neurodegenerative disorders, and cancer. Therefore, regulating dysfunctional mitochondria represents a pivotal therapeutic opportunity in biomedicine. Marine ecosystems are biologically very diversified and harbor a broad range of organisms, providing both novel bioactive substances and molecules with meaningful biomedical and pharmacological applications. Many mitochondria-targeting marine-derived molecules have been described to regulate mitochondrial biology, thus exerting therapeutic effects by inhibiting mitochondrial abnormalities, both in vitro and in vivo, through different mechanisms of action.

mitochondria disease therapy marine natural products marine organisms

1. Introduction

Several marine-derived drugs have been highlighted to target mitochondria or mitochondrial signaling pathways and could thus counteract pathological processes in many human diseases, including neurodegenerative diseases, metabolic disorders, cancer proliferation, and metastasis.

The following text will discuss the recent advances in biomedical strategies to treat human diseases by harnessing mitochondrial function and/or dynamics using marine resources. It will exclusively focus on biomolecules derived from marine organism and therapeutic strategies that target mitochondria, ranging from mitochondrial biogenesis to mitochondrial degradation (summarized in **Table 1** and **Table 2** and **Figure 1**).

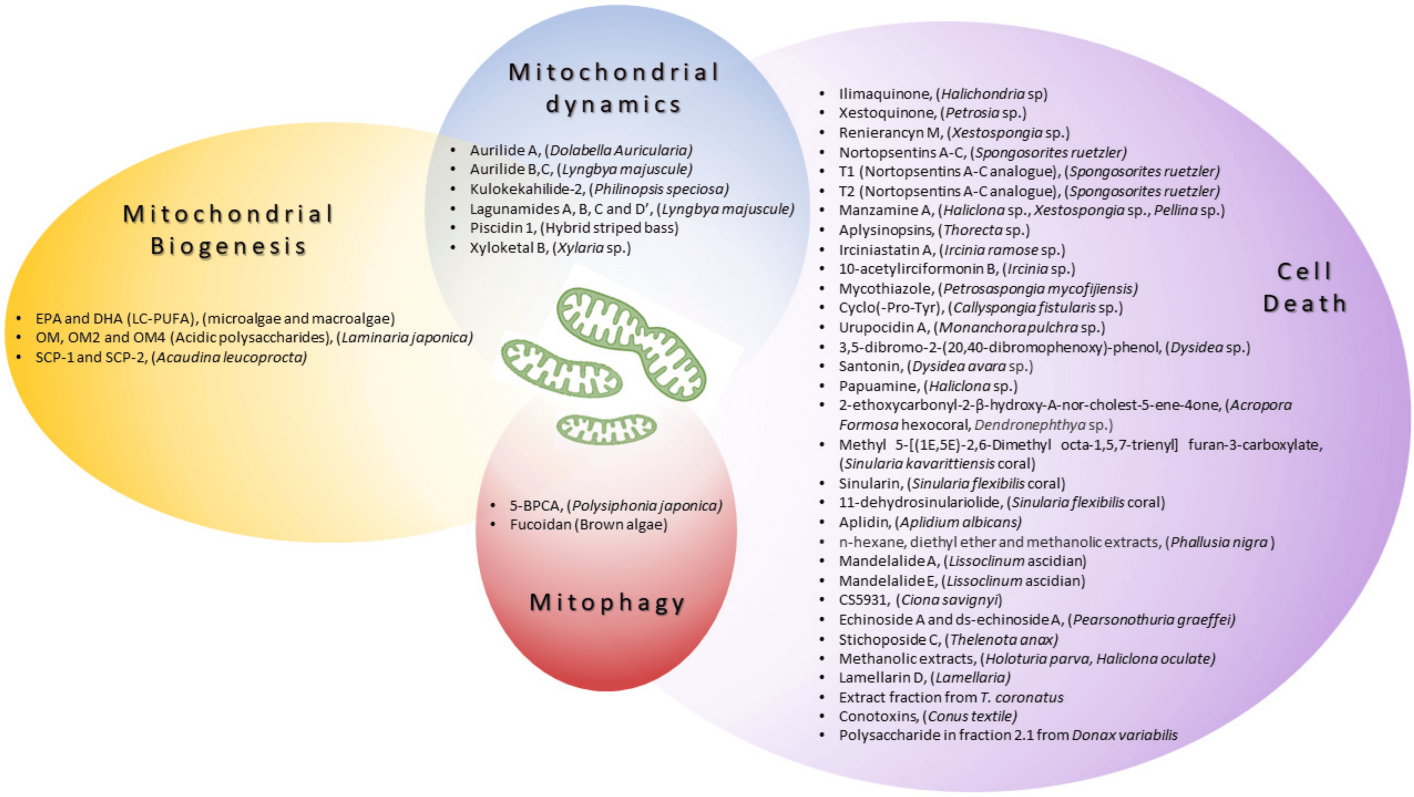

Figure 1. A schematic representation of compounds derived from marine organisms described as biomodulators of specific mitochondrial processes (mitochondrial biogenesis and dynamics) or cellular events involving mitochondria (mitophagy and cell death). Special emphasis should be placed on the modulators of cell death because of their potential as anticancer drugs.

Table 1. Mitochondrial modulators from marine resources acting on mitochondrial biogenesis, mitochondrial dynamics, and mitophagy. ↑ indicates increase and ↓ indicates decrease.

Compound(s)	Marine Organism	Mechanism of Action Regarding Mitochondria	Cell Line or Model of Disease Used in Preclinical Studies
Mitochondrial Biogenesis			
n-3 PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)	Microalgae and macroalgae	↑PGC1-α, ↑NRF1, ↑mitochondrial biogenesis	C57BL/6J epididymal fat [1]
oligomannuronate (OM) and OM-chromium (III) complexes (OM2 and OM4)	*Laminaria japonica*	↑PGC1-α, ↑mitochondrial function, ↑mitochondrial biogenesis	C2C12, 3T3-L1 [2]
SCP-1 and SCP-2	*Acaudina leucoprocta*	↑AMPK/PGC1-α, ↑NRF2, ↑mitochondrial biogenesis, ↓oxidative stress	Fatigue test in ICR mice [3]
Mitochondrial dynamics			

Compound(s)	Marine Organism	Mechanism of Action Regarding Mitochondria	Cell Line or Model of Disease Used in Preclinical Studies
Mitochondrial Biogenesis			
Aurilide A	*Dolabella auricularia*	Accelerate OPA-1 processing, mitochondrial fragmentation, and the release of CytC [4]	HeLa S3, NCI60 panel [5]
Aurilide B, C	*Lyngbya majuscule*		HCT-8, P388, A549, SK-OV-3, PC-3 [6]
Kulokekahilide-2	*Philinopsis speciosa*		P388, SK-OV-3, MDA-MB-435 [7]
Lagunamides A, B, C and D	*L. majuscule*		P388, A549, PC3, HCT8, SK-OV3, HCT8, MCF7 [8][9]
Piscidin-1	Hybrid striped bass	↓MFN1, ↓MFN2, ↓OPA1, ↓OXPHOS, ↑DRP1, ↑FIS1, ↑mtROS, mitochondrial dysfunction, apoptosis	MG63 [10][11]
Xyloketal B	*Xylaria* sp.	↑Drp1, ↓mitochondrial fregmentation, ↓mitochondrial superoxide production	In vitro model of ischemic stroke in PC12 [12]
Mitophagy			
5-BPCA	*Polysiphonia japonica*	The preservation of PARKIN expression and stabilization of mitochondrial morphology	Model of palmitate (PA)-induced lipotoxicity in a rat pancreatic β-cell line (Ins-1 cells) [13]
Fucoidan: treatment with Fucoidan nanoparticles loaded with proanthocyanidins	Brown algae	↑PINK1, ↑PARKIN, ↓mtDNA release	A model of cisplatin-induced damage in vitro (HK-2 cells) and in vivo (Kunming mice) [14]

indicates

Compound(s)	Marine Organism	In Vitro/In Vivo Models	Mechanism of Action Regarding Mitochondria	Disease Area
Ilimaquinone	*Halichondria* sp.	MCF-7, MDA-MB-231	caspase activation, ↑ROS, ↓Δψm	Breast cancer [15]
Xestoquinone	*Petrosia* sp.	Molt-4, K562, Sup-T1	↑ROS, ↓HSP90	Leukemia [16]
Renieranycin M	*Xestospongia* sp.	H460	↑BAX, ↓MCL1, ↓BCL2, caspase activation	Lung cancer [17][18]
Nortopsentins A-C	*Spongosorites ruetzler*	P388 cells	caspase activation	Leukemia [19]

Compound(s)	Marine Organism	In Vitro/In Vivo Models	Mechanism of Action Regarding Mitochondria	Disease Area
T1 (Nortopsentins A-C analogue)	*Spongosorites ruetzleri*	HCT-116 colorectal cancer cells	caspase activation, ↑mitochondrial trans-membrane potential	Colon cancer [20]
T2 (Nortopsentins A-C analogue)	*Spongosorites ruetzleri*	HCT-116 colorectal cancer cells	caspase activation, ↑mitochondrial trans-membrane potential	Colon cancer [19]
Manzamine A	*Haliclona* sp., *Xestospongia* sp., *Pellina* sp.	HCT116 cells	↓BCL2, Δψm loss, ↑caspase activation, CytC release,	Colon cancer [21]
Aplysinopsins	*Thorecta* sp.	K562 cells	↓BCL2, Δψm loss	Leukemia [22]
Irciniastatin A	*Ircinia ramose* sp.	Jurkat cells	↑ROS, ↑JNK, ↑p38, apoptosis	Leukemia [23]
10-acetylirciformonin B	*Ircinia* sp.	HL 60 cells	↓BCL2, ↓Bcl-xL, ↑BAX, ↑ROS, CytC release, apoptosis	Leukemia [23]
Mycothiazole	*Petrosaspongia mycofijiensis*	T47D cells	↓HIF-1 signaling, ↓mitochondrial function	Breast tumor [24]
Cyclo(-Pro-Tyr)	*Callyspongia fistularis* sp.	HepG2 cell	↓BCL2, ↑BAX, ↑ROS, apoptosis	Hepatocellular carcinoma [25]
Urupocidin A	*Monanchora pulchra* sp.	PCa cells	Δψm loss, ↑ROS, CytC release, apoptosis	Prostate cancer [26]
3,5-dibromo-2-(20,40-dibromophenoxy)-phenol	*Dysidea* sp.	PANC-1	Complex II inhibition	Pancreatic carcinoma [27]
Santonin	*Dysidea avara* sp.	ALL B-lymphocytes	↓Δψm, ↑ROS, CytC release, apoptosis	Acute lymphoblastic leukemia [28]
Papuamine	*Haliclona* sp.	MCF-7	mitochondrial damage and JNK activation	Breast cancer [29]
2-ethoxycarbonyl-2-β-hydroxy-A-nor-cholest-5-ene-4one	*Acropora Formosa* hexocoral,	A549	↓ TNF-α, ↓IL-8, ↓Bcl2, ↓MMP2, ↓MMP9, ↑ROS, ↑	Lung cancer [30]

Compound(s)	Marine Organism	In Vitro/In Vivo Models	Mechanism of Action Regarding Mitochondria	Disease Area
	Dendronephthya sp.		BAX, ↑p21, CytC release	
Methyl 5-[(1E,5E)-2,6-Dimethyl octa-1,5,7-trienyl] furan-3-carboxylate	*Sinularia kavarittiensis* coral	THP-1	↓Bcl-xL, ↑BAX, ↑ROS, ↓Δψm, CytC release, apoptosis	Leukemia [31]
Sinularin	*Sinularia flexibilis* coral	SK-HEP-1	↑ROS, ↓Δψm,↓OXPHOS, apoptosis	Liver cancer [32] [33]
11-dehydro-sinulariolide	*Sinularia flexibilis* coral	Ca9-22	ΔΨm loss, ↑caspase-3/-9 ↑Bax, ↓Bcl-2/Bcl-Xl, CytC release, apoptosis	Melanoma [32]
Aplidin	*Aplidium albicans*	MOLT-4, NIH3T3	↑ROS, ↓Δψm, ↓ATP, apoptosis	Leukemia, Lymphoma [34][35]
n-hexane, diethyl ether and methanolic extracts	*Phallusia nigra*	Isolated mitochondria from skin tissue of melanoma induced albino/Wistar rats	mitochondrial swelling, ↑ROS, ↓Δψm, CytC release, apoptosis	Melanoma [36]
Mandelalide A	*Lissoclinum* ascidian	NCI-H460, Neuro-2A, HeLa cells	complex V inhibition, apoptosis	Lung cancer, Neuroblastoma [37]
Mandelalide E	*Lissoclinum* ascidian	NCI-H460, HeLa, U87-MG, HCT116	apoptosis	Lung cancer, Glioblastoma [38]
CS5931	*Ciona savignyi*	HCT-8	↑caspase-3, ↑caspase-9, ↑Bax, ↓Δψm, CytC release, apoptosis	Colon cancer [39]
Echinoside A and ds-echinoside A	*Pearsonothuria graeffei*	HepG2, mice	apoptosis	Hepatocarcinoma [40]
Stichoposide C	*Thelenota anax*	HL-60, K562, THP-1, NB4, SNU-C4, HT-29, CT-26; mouse CT-26 subcutaneous tumor and HL-60	↑Fas, ↑caspase-3, ↑caspase-8, cleavage of Bid, mitochondrial damage, apoptosis	Leukemia, Colorectal cancer [41]

Compound(s)	Marine Organism	In Vitro/In Vivo Models	Mechanism of Action Regarding Mitochondria	Disease Area
		leukemia xenograft models		
Methanolic extracts	*Holoturia parva*, *Haliclona oculate* sp.	Mitochondria isolated from a rat model of hepatocellular carcinoma	↑ROS, ↓Δψm, CytC release, ↑caspase-3, apoptosis	Hepatocellular carcinoma [42]
Lamellarin D	*Lamellaria*	p388	↓Bcl-2, ↓Δψm, ↑caspase-3, ↑caspase-9, apoptosis	Leukemia [43][44]
Extract fraction of *T. coronatus*	*Turbo coronatus*	EOC cells	↑ROS, ↓Δψm, CytC release, mitochondrial swelling, apoptosis and necrosis	Epithelial ovarian cancer [45]
Conotoxins	*Conus textile*	U87MG	↑ROS, ↓Δψm, CytC release, ↑caspase-3, ↑caspase-9, ↑Bax/Bcl-2	Glioma [46]
Polysaccharide in fraction 2.1	*Donax variabilis*	A549	Mitochondrial disfunction, ↓Δψm, CytC release, ↑caspase-3, ↑caspase-9, ↑Bax/Bcl-2, apoptosis	Lung cancer cells [47]

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their adaptation to this extreme environment, deep-sea species have the potential to produce a totally novel group of molecules with potent biological activities, bestowing an unexplored trove of novel therapeutically strategies to alleviate or treat many human diseases, including those caused by altered mitochondrial function or dynamics. Fortunately, the interest in natural products derived from deep-sea species is growing and will continue to do so in the next few years [50].

Despite yielding great advances in the field, several challenges still remain regarding the identification, characterization, and biomedical translation of novel marine organism-derived compounds acting on mitochondria. It is important to highlight that, often, the molecular mechanisms underlying the beneficial effects of many marine derived molecules that can potentially harness mitochondrial function and act as novel therapeutic entities are still unknown. As an example, a huge number of molecules derived from marine organisms have been described for their antioxidant effect; thus, it is speculated that they are likely acting on mitochondria, but a deeper knowledge on mitochondrial involvement is missing. An exception to this is represented by aurilides—drugs that induce apoptosis by interfering with mitochondrial dynamics and cristae organization—whose molecular mechanism of action has been exhaustively elucidated [4][51]. However, the molecular-resolution knowledge available for these drugs has not resulted in more applications at the translational level. This issue is further complicated because the experimental

data on molecular actors regulating mitochondrial dynamics, as well as data on the strong connection linking mitochondrial dynamics and function, are constantly increasing. Therefore, the identification of specific targets regulating mitochondrial biology is a field characterized by constant growth and remodeling [49].

Another important limitation for translational research in the field, shared by all the bioactive molecules derived from marine organisms, regardless of their molecular mechanism of action, is that the costs of production for these molecules is very high. Consequently, the characterization of the beneficial biomedical properties of many natural compounds derived from marine organisms remains stuck in the preliminary stage of in vitro testing, failing to reach the requirements for the sustainable implementation of in vivo pre-clinical and clinical trials (**Figure 2**). However, the technical and methodological tools and knowledge needed to produce bioactive metabolites from marine sources on an industrial scale started to emerge during the early 2000s, when research on natural, biomedical compounds attracted interest among scientific communities, as well as pharmaceutical companies. Strategies centered around producing natural compounds from marine bacteria, fungi, or microalgae are based on implementing culture, harvesting, and extraction procedures on a large scale [52]. This is much more complex for invertebrate sources, where only small amounts of pure compounds are achievable. For these organisms, random sampling directly from the natural environment is not acceptable from an ecological point of view. Moreover, the overall naturally available biomass would be sufficient for industrial demand. Aquaculture of medicine-producing marine invertebrates such as sponges, corals, oysters, or mussels represent a kind of solution to this limitation [53]. Importantly, the development of chemical synthesis also supported the strategies of production on an industrial scale, thus overcoming the issue of isolation from biomass. Synthetic strategies include the possibility of modifying the molecule of interest and developing derivatives with less complexity and more manageable properties. Moreover, the recently outlined genome sequencing approaches allow for an understanding of the biochemical mechanisms regulating the biosynthesis of specific compounds, helping their synthetic cloning. Synthetic biology approaches can also facilitate the generation of genetically modified microbial cell factories to produce heterologous bioactive molecules, including marine organism-derived compounds [54].

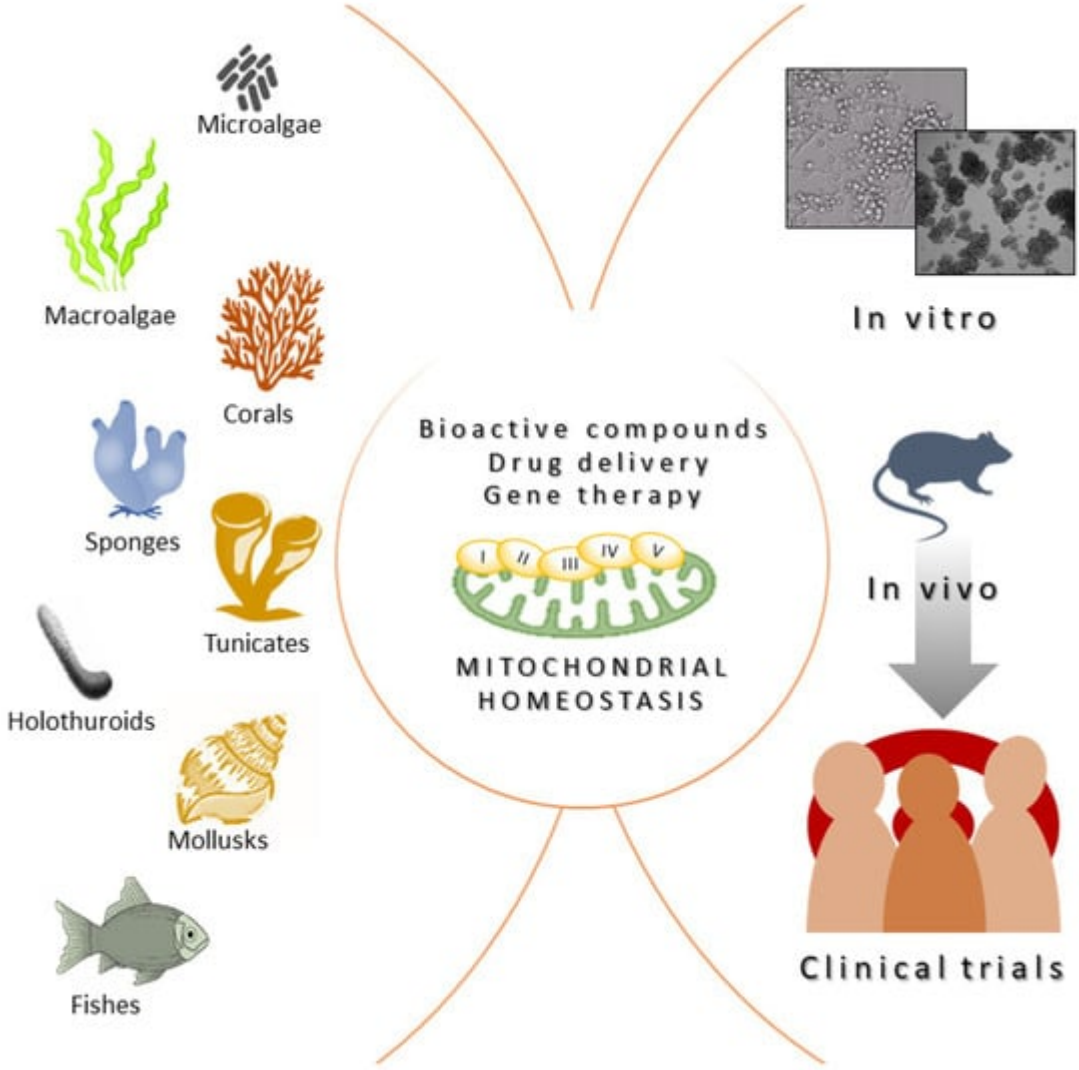

Figure 2. Marine organisms provide beneficial bioactive molecules that can modulate mitochondrial biology and recover mitochondrial homeostasis in pathological contexts. Bioactive compounds, molecules able to facilitate drug delivery, and marine species-derived therapeutic genes need to be tested in vitro (2D and 3D cell and organoid models) and in vivo before being involved in clinical trials with the ultimate aim of ameliorating patients' quality of life.

The process of bringing a drug candidate to the market requires extensive pre-clinical studies and clinical trials to determine the optimal doses, safety, and efficacy of the drug before it is approved by the FDA or the EMA. High costs in terms of money and time explain why only a handful of promising bioactive molecules will eventually reach the market and consumers. From the data gathered herein, clearly, the steps connecting the in vitro with the in vivo studies represent the main bottleneck in developing novel therapeutic techniques for mitochondrial illnesses using marine-derived compounds. A strong lack of extensive clinical trials hampers translational investigation in the field. This is the case for many marine-derived compounds that have shown bioactive properties to slow down cancer progression, mainly acting on proliferation. Most studies have been performed in vitro, without taking into account unintended secondary toxic effects on neighboring non-tumor cells or any systemic and non-systemic toxicity. Therefore, we are still far from assessing any safety, dosage, and efficacy issues in human clinical trials and

achieving the establishment of these types of compounds for use in precision medicine for patients affected by specific rare diseases.

Beyond in vitro 2D cell cultures, new and powerful tools to rapidly assess the potential efficacy of novel drugs are represented by three-dimensional (3D) organoids, which are emerging as promising models for precision medicine. They can be established rapidly and accurately mimic a patient's response to therapy [55]. However, the literature describing organoids as a tool to test marine-derived compounds acting on mitochondrial biology is practically non-existent. The researchers are convinced that using human organoids to create a first step of selection for the most promising marine organism-derived compounds to be used to regulate mitochondrial biology in human pathologies before going into organismic models may represent a useful way to accelerate biomedical translation.

This discussion underscores the importance of focusing on marine organism-derived compounds acting on mitochondrial function to design new treatments against a number of human pathologies with mitochondrial implications. They may act either alone or as adjuvants to gold-standard therapies, exerting synergistic effects in conjunction with conventional drugs. In this field of research, strong efforts should be made to develop well-controlled preclinical trials (in vivo in animal models and/or in vitro in human organoids) as well as clinical trials to assess the huge potential of marine agents in the prevention, treatment, and management of a wide range of human diseases with complex pathologies involving mitochondrial alterations, including neurodegeneration, metabolic diseases, and cancer.

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