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Review article

The potential of marine-derived compounds in geroscience

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ABSTRACT

Aging is a natural, multifactorial biological process characterized by progressive cellular and tissue damage in response to various stressors, leading to functional decline that often affects multiple organs, contributing to the development of age-related diseases. Although life expectancy has increased significantly, age-related conditions have become the leading causes of impairment and disability in the elderly, becoming a major global health concern. This highlights the need for innovative, multitarget strategies to modulate the aging process and extend healthspan. In recent years, researchers have explored natural solutions to counteract the hallmarks of aging. Among these, marine-derived molecules represent an up-and-coming niche of bioactive compounds, distinguished by their unique structural diversity and multifunctional properties. Marine products are increasingly studied for their antioxidant, anti-inflammatory and cytoprotective properties, targeting key pathways involved in aging, such as cellular senescence, genomic instability, impaired autophagy, and chronic inflammation. In this review, we aim to (i) explore the field of marine-derived bioactive molecules which demonstrated effects on lifespan extension, (ii) summarize studies showing their capacity to target one or more hallmarks of aging, (iii) highlight those that exhibit therapeutic potential in age-related diseases – including neurodegenerative, cardiovascular, metabolic, cancer, musculoskeletal, and chronic pulmonary disorders. Their multitarget activity makes them attractive candidates for the prevention or treatment of age-related diseases, and several have shown promising results in preclinical studies. However, only a limited number of these compounds have progressed to late-stage clinical trials, highlighting the need for further translational research, which may pave the way for novel anti-aging therapeutic strategies.

1. Introduction

Marine organisms represent a rich, although largely unexplored, resource of new molecules that can be exploited for their pharmacological potential. The unique features of the marine ecosystems (*e.g.* variations in temperature, oxygen concentrations, light, pressure, salinity, primary production) have shaped the marine life, generating the widest biodiversity worldwide. Among the various adaptive mechanisms, many marine species have evolved the production of specific primary and secondary metabolites as a strategy to survive in such a harsh and competitive environment, characterized by potent inhibitions of biological processes (Karthikeyan et al., 2022). Some examples include antifreeze proteins, which preserve blood from freezing in cold waters, and defensive metabolites ("chemical weapons"), to protect themselves against predators, pathogens, or other competitors (Karthikeyan et al., 2022). Such biologically active molecules are characterized by a wide diversity of chemical structures (Table S2), often previously undescribed in terrestrial habitats. The resulting high

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variety of possible biological targets and mechanisms of action leads to several pharmacological properties, *e.g.* anti-inflammatory, antibacterial, antiviral, antioxidant, anti-cancer, anticoagulant, antihypertensive, antidiabetic (Mayer et al., 2024). However, despite the high number of marine-derived drugs under preclinical investigation or phase I, II and III clinical trials, only seventeen are currently in the market, most of them for cancer treatment (Cappello and Nieri, 2021; Dyshlovoy and Honecker, 2022).

Marine-derived compounds can be synthesized *de novo* by the organism, either as genetically encoded proteins or as products of metabolic reactions; alternatively, they can be ingested through the diet or even synthesized by a symbiont microorganism. They can be extracted from organisms belonging to all levels of the evolutionary scale, from prokaryotes to higher animals. Compounds isolated from marine bacteria and fungi have long been studied, since they own unique chemical structures and cover a wide range of biological activities and therapeutic roles (Karthikeyan et al., 2022; Liming et al., 2016; Santos et al., 2020), but only a few have a consolidated use in clinical practice (Cappello and Nieri, 2021; Santos et al., 2020). Recently, unicellular microalgae have emerged as a novel reservoir of bioactive secondary metabolites, many of which, previously studied for their toxic potential, have now demonstrated various pharmacological properties and are increasingly involved in preclinical research (Pradhan and Ki, 2022). Macroalgae represent instead a well-established source of exclusive bioactive metabolites, including specific carbohydrates (*e.g.* fucoidans), peculiar photosynthetic pigments (*e.g.* fucoxanthin), as well as phenolic compounds and terpenoids (Polat et al., 2023). A few of them have been approved and commercialized or entered clinical trials (Polat et al., 2023). Among marine animals, sponges are extremely rich in bioactive compounds, mainly due to microbial symbionts which colonize their tissues, and they have been exploited for drug discovery purposes since the 1950s (Schwartsmann et al., 2001). Other marine invertebrates (*e.g.* cnidarians, molluscs, echinoderms, tunicates and ascidians) are valuable sources of bioactive compounds, among which some approved drugs (Romano et al., 2022). Molecules with pharmacological potential were also obtained from fishes, directly produced (*e.g.* fatty acids, peptides and protein hydrolysates) (Awuchi et al., 2022) or even introduced with food (*e.g.* the algal carotenoid astaxanthin).

In the last years, a novel application of marine-derived molecules is increasingly emerging, since several products revealed anti-aging properties and were proposed as potential tools to face the aging process (Han et al., 2024; X. Wang et al., 2021). Thus, there is growing interest in screening the sea to discover candidate molecules with the ability to interfere with aging (Hassane et al., 2020; Louka et al., 2021; Maglioni et al., 2021; Ruiz-Torres et al., 2018; H. Yang et al., 2023). Aging is a complex biological process characterized by the dysfunction of essential cellular pathways and metabolisms. Various interventions, such as pharmacological treatments, nutritional approaches, and lifestyle changes, can be employed to delay the onset of aging signs and promote longevity (Biga et al., 2025; López-Otín et al., 2023; Peto et al., 2025). Potentially, any chemical compound that interacts with aging pathways may be investigated for the prevention and treatment of aging, and the sea represents a rich reservoir to seek geroprotective compounds.

A deeper, comprehensive investigation of marine pro-longevity compounds necessitates considering also their absorption and distribution in the human body, which are facilitated by the presence of specific membrane transporters. Indeed, the FDA guidelines highlight the need to identify transporter(s) responsible for the delivery of new (and old) candidate drugs before starting the process of drug testing (Galetin et al., 2024). Therefore, the prediction and identification of the transporters involved in the flux of marine compounds from the sea environment to human body are essential for the application of marine-derived drugs in managing age-related disorders. Furthermore, membrane transporters may be considered not only as carriers for marine drug molecules, but also as specific or nonspecific targets (Galetin et al., 2024). Indeed, any molecule that interacts with a membrane transporter may potentiate or inhibit a metabolic pathway, which directly or indirectly affects longevity and age-related conditions. Altogether, the knowledge of the marine drug-transporter interactions will provide a more comprehensive view of the molecular pathways affected by these compounds, further enlarging the spectrum of their effects.

In this review, we described the potential roles of marine-derived molecules in delaying or improving the aging process. In the first part, we discussed the potentiality of marine molecules in promoting longevity, highlighting marine-derived compounds that experimentally extended the lifespan of model organisms; in the second, we explored compounds that target the main mechanisms involved in the aging progression, the so-called "hallmarks of aging"; lastly, we provided an overview of candidate drugs for the treatment of the main age-related diseases. When present, information on specific transporters for the mentioned marine compounds was provided.

2. Marine bioactive compounds and longevity

Seas and oceans host the most long-lived species: among the top 100 species with the highest longevity in the world, 70 are marine ones (*i.e.* sponges, bivalves, fish, polychaetes worms, marine mammals, sea urchins, crustaceans, and reptiles), most of which can live over 100 years (Table S1; Bodnar, 2009). The oldest animal on earth appears to be a specimen of the Antarctic sponge *Scolymastra joubini* (with an estimated age of 15,000 years), and an exceptional maximum lifespan was also recorded for the bivalve *Arctica islandica* (507 years) and the Greenland shark (392 years) (Table S1). Some marine species reach extreme longevity in the apparent lack of senescence, *e.g. A. islandica*, the rockfish *Sebasteus aleutianus* (205 years), the sea urchin *Strongylocentrotus franciscanus* (200 years) (Table S1; Bodnar, 2015; Gruber et al., 2015). Moreover, the ability to rejuvenate is restricted to a few marine animals, which reverse our knowledge of aging: a cnidarian species (*Turritopsis dohrnii*, the "immortal jellyfish") and the ctenophore *Mnemioipsis leidyi* undergo "reverse development", *i.e.* they rejuvenate from the adult to the larval stage, restarting their life cycle and achieving biological immortality (Pascual-Torner et al., 2022; Soto-Angel and Burkhardt, 2024). All those exceptional peculiarities of the marine environment suggest the presence of specific features leading to extreme longevity and successful aging, but the underlying reasons are not fully clarified. While for some species the longevity is attributable to ecological, physiological, or genetic factors, in other cases the mechanisms of long lifespan are still to be explored (Bodnar, 2009; Lagunas-Rangel, 2021; Polinski et al., 2020).

Several marine-derived compounds demonstrated a pro-longevity action by improving the lifespan in different model organisms (Table 1; Fig. 1; Table S2).

The cyclic lipopeptide kahalalide F and the macrocyclic antibiotic ikarugamycin, both of microbial origin, induced a significant increase of *Caenorhabditis elegans* lifespan by 10 % and 22 %, respectively (Maglioni et al., 2021; Wang et al., 2019). Kahalalide F, initially isolated from the sea mollusc *Elysia rufescens* and green algae and recently shown to have a microbial origin, has currently reached phase I and II clinical trials as an anti-cancer, demonstrating a safe profile (Wyer et al., 2022). Although its mechanism of action is not elucidated, Akt inhibition and the lysosomes were identified as possible targets (Maglioni et al., 2021; Wyer et al., 2022). While inducing lifespan extension, kahalalide F increased the resistance to heat shock and oxidative stress, and improved animal healthspan, measured as movement ability (Maglioni et al., 2021). Ikarugamycin, a macrocyclic antibiotic initially isolated from *Streptomyces phaeochromogenes*, was instead identified as an activator of the transcription factor EB (TFEB), inducing autophagy *in vitro* (see paragraph 3.2) and mitigating metabolic syndromes in mice, and its pro-longevity effect is possibly achieved through mimicking a starvation condition (Wang et al., 2019). Notably, caloric restriction is considered among the most effective strategies to reach longevity (Dorling et al.,

Table 1
Marine compounds with a demonstrated effect on lifespan extension. For each compound, the source, the model organism used for the survival study, and the percentage of lifespan extension are indicated.

MARINE COMPOUND	SOURCE	MODEL ORGANISM	LIFESPAN EXTENSION	REFERENCES
Kahalalide F	marine bacteria, *Elysia rufescens* (mollusk), green algae	*C. elegans*	10 % (% survival)	Maglioni et al., 2022
Ikarugamycin	*Streptomyces phaeochromogenes* (marine bacterium)	*C. elegans*	22 % (% survival)	Wang et al., (2017)
PTR−08 extract	*Pseudomonas sp* (marine bacterium)	*S. pombe*	n.a.	Prastya et al., (2020)
Fucoxanthin	Brown algae, diatoms	*C. elegans* *D. melanogaster*	14 % (mean) 24 % (max) 8–37 % (median)	Lashmanova et al., (2015)
Astaxanthin	microalgae, copepods	*C. elegans* *Tenebrio molitor* *S. cerevisiae* HET−3 mice	16–30 % (mean) 5–13 % (mean) 12 % (mean and max) n.a. 20–40 % 12 % (mean)	Yazaki et al., (2011) Fu et al., (2021) Ding and Zhao, (2022) Dhinaut et al., (2017) Sj et al., (2019) Harrison et al., (2024)
Fucoidan	*Sargassum fusiforme* (macroalgae)	*D. melanogaster*	10–24 % (mean)	Zhang et al., (2019)
Porphyran	*Porphyra haitanensis* (macroalgae)	*D. melanogaster*	6–8 % (mean)	Zhao et al., (2008)
GP polysaccharide	*Gracilaria lemaneiformis* (macroalgae)	*C. elegans*	16.47 % (mean)	Wang et al., (2019)
A. spicifera extract	*Acanthophora spicifera* (macroalgae)	rotifers	9–14 %	Snare et al., (2013)
CFH (hydrolysate)	*Cucumaria frondosa* (sea cucumber)	*D. melanogaster*	12.0–17.7 % (mean) 15.1–27.8 % (max)	Lin et al., 2018
SVH (hydrolysate)	*Stichopus variegates* (sea cucumber)	*D. melanogaster*	10.6–15.5 % (mean) 11.4–24.8 % (max)	Lin et al., (2020)
AjPH (protein hydrolysate)	*Apostichopus japonicus* (sea cucumber)	*C. elegans*	18.51 % (mean)	Guo et al., (2020)
SCPs (peptides)	*Acaudina leucoprocta* (sea cucumber)	*C. elegans*	31.46 % (mean)	Wu et al., (2022)
AMH (hydrolyzate)	*Actinopyga miliaris* (sea cucumber)	*C. elegans*	57.79 % (mean)	Chen et al., (2023)
MP (peptides)	*Mytilus edulis* (bivalve)	*C. elegans*	15.8 % (mean)	Zhou et al., (2018)
D2-G1S−1 and D2-G1S−2 (peptides)	*Arca subcrenata* (bivalve)	*C. elegans*	10.91–32.73 (mean)	Shi et al., (2021)
CSSP (peptides)	*Lutjanus erythropterus* scales (fish)	*D. melanogaster*	21.2–26.2 % (mean)	S. Chen et al., (2020)
MCP (marine collagen peptides)	*Oncorhynchus keta* skin (fish)	rats	7.6–14.7 % (mean of last 30 % survivors)	Liang et al., (2010)
P5 peptide	*Decapterus maruadsi* (fish)	*C. elegans*	34.39 % (mean)	H. Chen et al., (2020)
Marine cholesterol, brassicasterol, crinosterol, 24-methylenecholesterol	*Mytilidae* (bivalve)	*S. cerevisiae*	n.a.	Sun et al., (2014)

2020). Although bacterial molecules tested for a pro-longevity effect are still few, their huge potential deserves further investigations, as suggested by a recent screening of marine *Pseudomonas* sp. extracts (PTR-08), which revealed the ability to promote yeasts longevity (Prastya et al., 2020).

Macro- and microalgae represent a promising source of molecules with a pro-longevity effect. Fucoxanthin, produced by brown algae (*e.g. Undaria pinnatifida*) and microalgae (*e.g.* the diatoms *Phaeodactylum tricornutum*), and astaxanthin, isolated from several marine sources (microalgae, algae, krill, shrimps and fish), are xanthophyll carotenoids with potent antioxidant properties and an extremely safe profile, and are widely studied for their beneficial effects on aging in different models (Fig. 1, Tables 1–2). Fucoxanthin has been described to regulate the expression of ABC transporters (Chandra et al., 2023), while astaxanthin intestinal absorption occurs via the fatty acid transporter CD36 (Cluster of Differentiation 36) with high affinity (Zhang et al., 2024). The role of CD36 seems to be fundamental for the distribution of astaxanthin, which is a poorly soluble carotenoid. Fucoxanthin extended the lifespan of both *Drosophila melanogaster* and *C. elegans* (Lashmanova et al., 2015), an effect associated with changes in the expression of genes related to longevity (Moskalev et al., 2018). Astaxanthin prolonged longevity in *C. elegans* (Ding and Zhao, 2022; Fu et al., 2021; Yazaki et al., 2011), in antioxidant-deficient and DNA-repair-deficient strains of the yeast *Saccharomyces cerevisiae* (Sj et al., 2019; Sudharshan and Dyavaiah, 2021), and in an insect model (the beetle *Tenebrio molitor*), but only after an immune challenge (Dhinaut et al., 2017). The pro-longevity effect of astaxanthin was ascribed to its ability to protect against oxidative stress and to activate autophagic pathways (Fu et al., 2021; Sj et al., 2019; Sudharshan and Dyavaiah, 2021) (Figs. 2–3). Recently, astaxanthin's pro-longevity potential was explored in a robust lifespan study

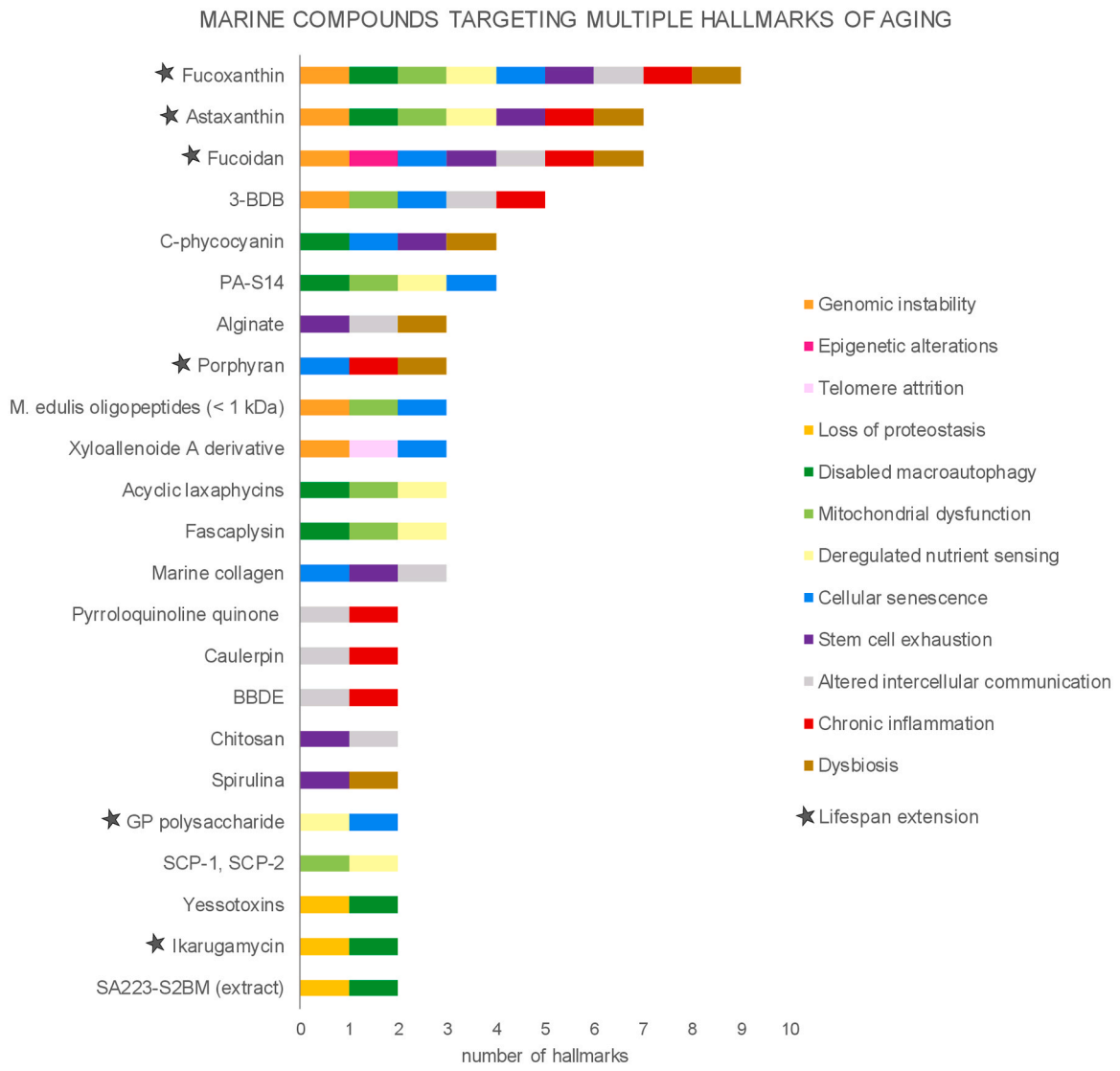

Fig. 1. *Marine molecules targeting multiple hallmarks of aging.* This chart visually highlights the multitarget potential of marine molecules and their relevance in aging. The y-axis lists marine molecules reported to modulate more than one hallmark of aging, while the x-axis indicates the number of hallmarks targeted. Colored squares represent individual hallmarks, as specified in the adjacent legend. A star next to a compound's name denotes experimentally demonstrated lifespan extension in at least one model organism.

performed on mice by the Interventions Testing Program (ITP, National Institute of Aging), widely recognized as the most reliable program in the research on longevity treatments. The results of the study demonstrated that astaxanthin extended the median lifespan of male mice by 12 % (Harrison et al., 2024). Notably, this effect was observed in an outbred, genetically heterogeneous mouse strain (UM-HET3), enforcing the potential to translate the result to humans.

Among macroalgal products, the red alga *Acanthophora spicifera* was shown to induce a lifespan increase in rotifers (Snare et al., 2013), and the polysaccharides fucoidan, porphyran and the *Gracilaria lemaneiformis* polysaccharide (GP) extended *D. melanogaster* or *C. elegans* lifespan (Wang et al., 2019; Zhang et al., 2019; Zhao et al., 2008). Fucoidan, extracted from the brown algae *Sargassum fusiforme*, exhibited a strong activity against oxidative stress *in vitro* and in flies, where the lifespan extension was shown to be mediated by the Nrf2 antioxidant signaling pathway (Zhang et al., 2019). Besides being an antioxidant, this algal polysaccharide has a wide variety of biological activities (*e.g.* anti-inflammatory, anticoagulant, antithrombotic, immunoregulatory, antiviral, antitumor, and modulatory of microbiota), demonstrating a great potential in aging research. Among molecular targets of fucoidan, the ABC transporter ABCA1 (Mirza et al., 2023) and the SLC transporter OCT2 (Wu et al., 2017) have also been listed. In both cases, fucoidan increased the surface expression and the functionality of the mentioned transporters, acting as an atheroprotective compound (see Paragraph 4.2). A recent study described the ability of fucoidan to inhibit the organic solute transporters SLC51A and B, ameliorating the hepatorenal syndrome (Zhao et al., 2023), further enlarging the role of marine compounds in managing also co-morbidities that may occur in aging. Porphyran, isolated from red algae of the genus *Porphyra*, is known for its antioxidant, immunomodulatory and hypolipidemic activities. Both natural porphyran and some of its degraded forms were effective in improving the fly's longevity, both in normal metabolic conditions and during heat stress, with an effect dependent on the different molecular weights (Zhao et al., 2008). The anti-aging effect of the GP polysaccharide was demonstrated in *C. elegans*, with prolonged lifespan and healthspan (assessed as maintenance of the reproductive capacity). Interestingly, such effect was mediated by the DAF-16 protein (Wang et al., 2019), a key regulator of longevity in the nematodes and homologue of the mammalian forkhead box O (FOXO), one of the main downstream target of the insulin/insulin-like growth factor-1 signaling

Table 2
Marine-derived compounds with the ability to target the hallmarks of aging. For each compound, the source, the primary mechanisms of action, and the target hallmarks of aging are indicated. Compounds capable of extending the lifespan are highlighted in bold.

MARINE COMPOUND	SOURCE	MECHANISMS OF ACTION	TARGET HALLMARKS OF AGING	REFERENCES
14-norpseurotin A	*Talaromyces helicus* (marine fungus)	Reduction of TNF-α, IFN-γ (pro-inflammatory) Increase of IL−4, IL−10 (anti-inflammatory)	Chronic inflammation	Qiu et al., (2024)
2,7″-phloroglucinol−6,6′-bieckol (PHB)	*Ecklonia clava* (brown alga)	Improvement of hormone regulation (increase of IGF1)	Altered intercellular communication	Kim et al., (2021)
3-Bromo−4,5-dihydroxybenzaldehyde (3-BDB)	red algae	Antioxidant, decreased ROS Reduction of DNA damage Ripolarization of mitochondrial membrane potential SASP improvement (inhibition of IL−6, TNF-α, INF-γ)	Cellular senescence Mitochondrial dysfunction Genomic instability Altered intercellular communication Chronic inflammation	Zhen et al., (2023) Kang et al., (2017)
3-bromo−4,5-dihydroxybenzyl ether (BBDE)	*Polysiphonia urceolata*	SASP improvement (reduced IL−6, IL−1β, TNF-α)	Altered intercellular communication Chronic inflammation	Choi et al., (2018)
6,8-di-O-acetylmalyngamide 2	*Moorea producens* (marine cyanobacterium)	Activation of AMPK Increase in glucose uptake	Deregulated nutrient sensing	Sueyoshi et al., (2017)
Acyclic laxaphycins	*A. torulosa* (marine cyanobacteria)	Activation of AMPK Inhibition of mTOR Activation of autophagy Modulation of mitochondrial membrane potential	Disabled macroautophagy Deregulated nutrient sensing Mitochondrial dysfunction	Alvariño et al., (2020)
Aglycon of rhizochalin	*Rhizochalina incrustata* (sponge)	Activation of AMPK Inhibition of mTOR	Deregulated nutrient sensing	Khanal et al., (2011)
Alginate	brown algae	Anti-inflammatory Scaffold function (improvement of ECM health, cell infiltration, nutrient transport) Increase of intestinal *Akkermansia*, *Alloprevotella*, *Bacteroides*, *Lactobacillus*, *Enterorhabdus, Weissella*	Stem cell exhaustion Altered intercellular communication Dysbiosis	Saludas et al., (2017) Mann et al., 2016 Cattelan et al., (2020) Liu et al., (2021)
Apratoxin A	*Moorea producens* (cyanobacterium)	Activation of autophagy (ER-stress independent)	Disabled macroautophagy	Dyshlovoy, (2020)
Astaxanthin	microalgae, copepods	Antioxidant Reduction of DNA oxidative damage Activation of autophagy Inhibition of Akt and mTOR Activation of FOXO3 Inhibition of IGF1 Improvement of mitochondrial integrity, mitochondrial membrane potential, mitochondrial content and activity Reduction of mitochondrial ROS production and depolarization Upregulation of stemness genes (OCT4, SOX2, Nanog, KLF4) Downregulation of NF-κB, COX−2, iNOS Reduction of pro-inflammatory cytokines Increase of intestinal *Akkermansia* and SCFAs (acetate) Improvement of colon tight junction	Genomic instability Disabled macroautophagy Deregulated nutrient sensing Mitochondrial dysfunction Stem cell exhaustion Chronic inflammation Dysbiosis	Sudharshan and Dyavaiah, (2021) Fu et al., (2021), Fu et al., (2023) Kim and Kim, (2018) Xue et al., (2017) Kim et al., (2010a) Kohandel et al., 2022
Astrogorgols	*Astrogorgia sp* (gorgonian)	Inhibition of ALK and IGF1R	Deregulated nutrient sensing	Lai et al., (2011)
C. gloeobotrydiformis polysaccharide	*Coccomyxa gloeobotrydiformis* (green alga)	Reduction of pro-inflammatory cytokines Increase of IL−10	Chronic inflammation	Dai et al., (2019)
C. samarensis metanolic extract	*Callyspongia samarensis* (sponge)	Activation of AMPK	Deregulated nutrient sensing	Resuello et al, (2020)
C. tuberculata extract	*Cotylorhiza tuberculata* (jellyfish)	GJIC improvement	Altered intercellular communication	Leone et al., (2013)
C. vasculum-derived compounds	*Cribrochalina vasculum* (sponge)	Inhibition of IGF1-R signaling	Deregulated nutrient sensing	Zovko et al., (2016)
Candidusin A	*Aspergillus candidus* (marine fungus)	Activation of AMPK activation Decrease in lipids	Deregulated nutrient sensing	Chen et al., (2023)

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Table 2 (*continued*)

MARINE COMPOUND	SOURCE	MECHANISMS OF ACTION	TARGET HALLMARKS OF AGING	REFERENCES
Caulerpin	*Caulerpa sp* (green algae)	SASP improvement (reduced IL−6, IL−17, IFN-γ, TNF-α) Reduction of NF-κB Reduction of leukocyte migration	Altered intercellular communication Chronic inflammation	Lucena et al., 2018
Cembranolide diterpene	*L. cristagalli* (soft coral)	Inhibition of farnesyl transferase	Genomic instability	Coval et al., (1996)
Chitosan	squid pens	Anti-inflammatory Scaffold function (improvement of ECM health, cell infiltration, nutrient transport)	Stem cell exhaustion Altered intercellular communication	Carvalho et al., (2023)
Clionamines	*Cliona celata* (sponge)	Activation of autophagy Ligand of phosphatidylinositol 4-kinase	Disabled macroautophagy	Persaud et al., 2022
Coibamide A	*Leptolyngbya sp* (cyanobacterium)	Activation of autophagy (ER-stress independent)	Disabled macroautophagy	Dyshlovoy, (2020)
C-phycocyanin	*Spirulina platensis* (cyanobacterium)	Antioxidant Activation of autophagy Inhibition of PI3K/Akt/mtor Interaction with the protein acyltransferase ZDHHC5 Increase of GM diversity Reduction of intestinal Bacteroidetes and increase of Firmicutes Improvement of gut barrier	Cellular senescence Stem cell exhaustion Disabled macroautophagy Dysbiosis	Liu et al., (2023) Liu et al., (2016) Liao et al., (2016) Xie et al., (2019)
Cromomycin A2	*Streptomyces sp* (marine bacterium)	Activation of autophagy Activation of TP53 family members	Disabled macroautophagy	Dyshlovoy, (2020)
D2-G1S−1 and D2-G1S−2	*Arca subcrenata* (bivalve)	Downregulation of AGE−1/PI3K and upregulation of DAF−16/FOXO Antioxidant	Deregulated nutrient sensing	Shi et al., (2021)
Dieckol	*Ecklonia clava* (brown alga)	Improvement of hormone regulation (increase of IGF1)	Altered intercellular communication	Kim et al., (2021)
Dihydrotrichodimerol	*Acremonium citrinum* (marine fungus)	PPARa/g binding Activation of Sirt1 and AMPK activation Decrease in lipids	Deregulated nutrient sensing	Liu et al., (2023)
Diphlorethohydroxycarmalol (DPHC)	*Ishige okamurae* (brown alga)	Inhibition of NF-κB	Chronic inflammation	Kang et al., (2015)
Ergosterol peroxide	*Phoma sp* (marine fungus)	ROS-dependent autophagy, Inhibition of mTOR, Akt and HSP27	Disabled macroautophagy	Wu et al., (2018)
Fascaplysin	*Fascaplysinopsis sp* (sponge)	Activation of autophagy Increase of p8 protein and ROS Inhibition of PI3K/AKT/mTOR signaling (indirect) Activation of AMPK and PGC−1α	Disabled macroautophagy Deregulated nutrient sensing Mitochondrial dysfunction	Dyshlovoy, (2020) Kumar, 2015 Oh et al., 2017
Flaccidoxide−13-acetate	*Sinularia gibberosa* (coral)	Inhibition of PI3K/Akt/mTOR pathway	Disabled macroautophagy	Wu et al., (2020)
Fucoidan	*F. distichus* (brown algae)	Activation of Sirt1, Sirt3 and Sirt6 Histone H3K9 deacetylation Enhanced DNA repair Reduced senescence markers SASP improvement Activation of FAK-Akt-TWIST pathway Scaffold function (improvement of ECM health, cell infiltration, nutrient transport) Downregulation of NF-κB, COX−2 and iNOS Increase of intestinal *Bacteroides*, *Faecalibacterium, Blautia Roseburia, Ruminococcus, Clostridium, Dorea, Eubacterium, Lachnobacterium* and *Bifidobacterium*	Genomic instability Epigenetic alterations Cellular senescence Stem cell exhaustion Altered intercellular communication Chronic inflammation Dysbiosis	Yu et al., 2017 Zheng et al., (2018); Yu et al., (2020) T. Wang et al., (2016) Rahnasto-Rilla et al., (2017) L. Zhang et al., (2022) Lee et al., (2016) Lee et al., (2018) Kim et al., (2015) Carvalho et al., (2023) Wu et al., (2021) S. Wang et al., (2023)
Fucoxanthin	Brown algae, diatoms	Antioxidant Activation of autophagy Activation of Nrf2 pathway Activation of Sirt1 and AMPK Upregulation of UCP Upregulation of Cx43 and Cx32, improvement of GJIC Downregulation of NF-κB	Genomic instability Disabled macroautophagy Deregulated nutrient sensing Mitochondrial dysfunction	Zhang et al., (2017) Chang et al., 2018 Woo et al., (2009) Chen et al., (2021) Suwanmanee et al., (2023) Liu et al., (2009)

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Table 2 (*continued*)

MARINE COMPOUND	SOURCE	MECHANISMS OF ACTION	TARGET HALLMARKS OF AGING	REFERENCES
		Reduction of COX−2, iNOS, PGE2, NO, IL−1β, IL−6, TNF-α Increase of GM diversity and F/B ratio Increase of intestinal *Lactobacillaceae* and *Lachnospiraceae*	Cellular senescence Stem cell exhaustion Altered intercellular communication Chronic inflammation Dysbiosis	Kim et al., (2010) Yang et al., 2020 Yang et al., (2024)
Gombasterols A–F and clathriol	*Clathria gombawuiensis* (sponge)	Activation of AMPK Increase in glucose uptake	Deregulated nutrient sensing	Woo et al., (2017)
GP polysaccharide	*Gracilaria lemaneiformis* (macroalga)	p16 and p53 downregulation (speculated) regulation of DAF−16/FOXO	Cellular senescence Deregulated nutrient sensing	Wang et al., (2022)
Halichondramide	*Chondrosia corticata* (sponge)	Inhibition of mTOR pathway	Disabled macroautophagy	Bae et al., (2013)
Hamacanthins	marine sponges	Inhibition of PI3K, Akt and mTOR	Disabled macroautophagy	Kim et al., (2013)
Hyrtiosal	*Hyrtios erectus* (sponge)	ECM improvement (reduced TGF-β/Smad2 signaling) Inhibition of PTP1B	Altered intercellular communication	Sun et al., (2007)
Ikarugamycin	*S. phaeochromogenes* (marine bacterium)	Activation of TFEB Inhibition of mTOR Activation of autophagy	Loss of proteostasis Disabled macroautophagy	Wang et al., (2017)
Ilimaquinone	*Hippospongia metachromia* (marine sponge)	Activation of TP53 family members Activation of autophagy	Disabled macroautophagy	Dyshlovoy, (2020)
Isofistularin−3	*A. aerophoba* (sponge)	DNA methyltransferase (DNMT)1 inhibitor Activation of autophagy	Disabled macroautophagy	Dyshlovoy, (2020)
Jaspine B derivatives	*Pachastrissa sp*, *Jaspis sp* (sponge)	Activation of JNK and Nrf2 Activation of autophagy Changes in mitochondrial potential	Disabled macroautophagy	Dyshlovoy, (2020)
Laminarin	brown algae	Inhibition of IGF1-R signaling	Deregulated nutrient sensing	Park et al., (2012)
Luminacin	*Streptomyces sp* (marine yeast)	Inhibition of JNK/p38/Akt Activation of autophagy	Disabled macroautophagy	Dyshlovoy, (2020)
M. edulis oligopeptides (< 1 kDa)	*Mytilus edulis* (bivalve mollusc)	Activation of Sirt1 Increased glutathione Modulation of mitochondrial membrane potential	Genomic instability Mitochondrial dysfunction Cellular senescence	Zhou et al., (2014)
Malformin A_1	*A. tubingensis* (marine fungus)	Increase of H3K9me3 and H4K16ac	Epigenetic alterations	Notarte et al., (2017)
Mandelalide A	*Lissoclinum ascidian* (tunicate worm)	Inhibition of mitochondrial ATP synthase Activation of AMPK	Deregulated nutrient sensing	Mattos et al., (2022)
Marine collagen	fish skin	Scaffold function (improvement of ECM health, cell infiltration, nutrient transport) Downregulation of MMP1	Cellular senescence Stem cell exhaustion Altered intercellular communication	Bourdon et al., (2021) Lim et al., (2019)
Meroterpene (AMT-E)	*Cystoseira usneoides* (brown alga)	Reduction of COX−2 expression and myeloperoxidase activity	Chronic inflammation	Zbakh et al., (2016)
MP	*Mytilus edulis* (bivalve)	Regulation of DAF−2/ and DAF−16/FOXO	Deregulated nutrient sensing	Zhou et al., (2018)
NA extract	*P. varicosa* (nudibranch)	Inhibition of mTOR	Disabled macroautophagy	Ruiz-Torres et al., (2018)
Nigrosporins B	*Nigrospora orza* (marine fungus)	Activation of autophagy Inhibition of PI3K/AKT/mTOR pathway	Disabled macroautophagy	J. Zhang et al., (2022)
Petromurin C	*Aspergillus candidus* (marine fungus)	Activation of autophagy Decrease in mitochondrial membrane potential	Disabled macroautophagy	Dyshlovoy, 2020
Phlorogucinol	Brown algae	ECM improvement (increased Notch2 and Oct4)	Altered intercellular communication	Kim et al., (2015)
Phorbaketal A	*Phorbas sp* (sponge)	Downregulation of NF-κB Inhibition of iNOS expression Reduction of NO, IL−1β, TNF-α, MCP−1	Chronic inflammation	Seo et al., (2015)
Piericidin analogue S14 (PA-S14)	*Streptomyces* (marine bacteria)	Activation of liver kinase B1 and AMPK Activation of autophagy	Disabled macroautophagy Mitochondrial	Liu et al., (2022)

(*continued on next page*)

Table 2 (*continued*)

MARINE COMPOUND	SOURCE	MECHANISMS OF ACTION	TARGET HALLMARKS OF AGING	REFERENCES
			dysfunction Deregulated nutrient sensing Cellular senescence	
Porphyran	*Porphyra haitanensis* (red alga)	Reduction of oxidative stress Downregulation of NF-κB Reduction of inflammatory cytokine Increase of intestinal *Roseburia* and *Eubacterium*	Cellular senescence Chronic inflammation Dysbiosis	Z. Zhang et al., (2018) Pradhan and Ki, 2022 H. Wang et al., (2023)
Porphyranase	*Zobellia galactanivorans* (marine bacterium)	Degradation of porphyran	Dysbiosis	Cian et al., (2015)
Psammaplin A	*Psammaplysilla sp* (marine sponge)	Activation of autophagy Activation of TP53 family members	Disabled macroautophagy	Dyshlovoy, 2020
Pyrroloquinoline quinone	marine bacteria	Improvement of hormone regulation (increase of IGF1 and BFGF expression) SASP improvement (reduction of IL−1β and TGF-β)	Altered intercellular communication Chronic inflammation	X. Wang et al., (2021)
S. glaucum steroids	*Sarcophyton glaucum* (soft coral)	ECM improvement (reduced TGF-β)	Altered intercellular communication	Tammam et al., (2023)
SA223-S2BM (extract)	*S. arenicola* (marine bacterium)	Upregulation of proteasomal proteins and chaperones Activation of autophagy	Loss of proteostasis Disabled macroautophagy	Louka et al., 2021
Sarcodiotheca gaudichaudii and *Chondrus crispus* powder	*S. gaudichaudii* and *C. crispus* (red algae)	Increase in intestinal *Bifidobacterium* Increase in circulating SCFAs Improvement of gut barrier	Dysbiosis	Cian et al., (2015)
SCP−1, SCP−2	*Acaudina leucoprocta* (sea cucumber)	Activation of AMPK Upregulation of mitochondrial proteins (TFAM, mtCOX) Upregulation of PGC−1α	Mitochondrial dysfunction Deregulated nutrient sensing	Q. Wang et al., (2021)
SCPs	*Acaudina leucoprocta* (sea cucumber)	Downregulation of DAF−2/insulin-IGF1 receptor Upregulation of DAF−16/FOXO Antioxidant	Deregulated nutrient sensing	Wu et al., (2022)
Sesquiterpenes	*Dactylospongia metachromia* (sponge)	Inhibition of ALK and IGF1R	Deregulated nutrient sensing	Daletos et al., (2014)
SF−5629 secondary metabolites	*Penicillium* SF−5629 strain (marine fungi)	Reduction of iNOS and COX−2 expression Reduction of PGE2 and NO Downregulation of NF-κB	Chronic inflammation	Ngan et al., (2017)
SH−82-EA-LM, 100-EA-LM and SH−100-MeOH-SM (extracts)	*M. fluostatin, B. licheniformis* (marine bacteria)	Activation of Sirtuin 1	Genomic instability	Hassane et al., (2020)
Spirulina	*Spirulina platensis* (cyanobacterium)	Anti-inflammatory Increase in lactic acid bacteria growth	Stem cell exhaustion Chronic inflammation Dysbiosis	Bachstetter et al., (2010) Finamore et al., (2017)
Spongolactams	*Spongia* sp (sponge)	Inhibition of farnesyl transferase	Genomic instability	Mori et al., (2007)
Stellettin B	*J. stellifera* (sponge)	Inhibition of PI3K/Akt/mTOR	Disabled macroautophagy	R. Wang et al., (2016)
Thiaplidiaquinones A and B	*A. conicum* (ascidian)	Inhibition of farnesyl transferase	Genomic instability	Cadelis et al., (2017)
Xyloallenoide A derivative (C3 *alias* Sirt1 activator 1)	*Xylaria sp* (mangrove fungus)	Sirt1 activation Activation of telomerase Inhibition of AMPK Activation of Akt	Genomic instability Telomere attrition Cellular senescence	Yang et al., (2023)
Yessotoxins	dinoflagellates (microalgae)	Activation of UPR and eIF2α Inhibition of mTOR Activation of autophagy	Loss of proteostasis Disabled macroautophagy	Rubiolo et al., (2014) Korsnes et al., (2016)

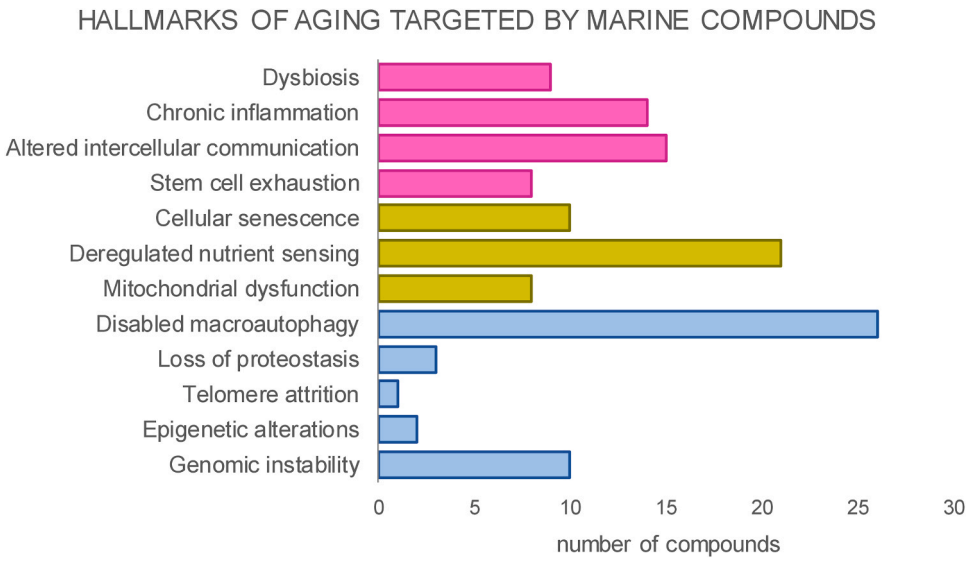

Fig. 2. *Hallmarks of aging targeted by marine-derived bioactive compounds.* This representation illustrates the distribution of marine compounds across different biological processes involved in aging. The y-axis lists the individual hallmarks of aging, while the x-axis indicates the number of marine compounds reported to target each hallmark. Please note that the bar corresponding to the hallmark *chronic inflammation* includes only the compounds cited in the present review: due to the hundreds of marine compounds with anti-inflammatory properties, the representation and description of their totality would deserve a dedicated topic, which is beyond the scope of this review. Bars are color-coded based on the functional classification of each hallmark as follow: primary (blue), antagonistic (green), integrative (pink).

(IIS) (Libina et al., 2003), whose role in the aging processes is widely recognized (see Paragraph 3.3).

Marine peptides from animal sources demonstrated an attractive potential for anti-aging medicine, *e.g.* those extracted from several species of sea cucumbers, bivalves and fish. Peptide-rich hydrolysates from the sea cucumbers *Cucumaria frondosa* and *Stichopus variegates* significantly improved the longevity of *D. melanogaster*, with increases of mean and maximum lifespan up to 17.7 % and 27.8 %, respectively. In aging mice, although the effect on longevity was not explored, the oral administration of sea cucumber peptides induced a neuroprotective effect (improved learning and memory), accompanied by a reduced oxidative damage of brain and liver (Lin et al., 2020, 2018). The lifespan of *C. elegans* was prolonged by peptides/hydrolysates from other sea cucumber species, *Apostichopus japonicus, Acaudina leucoprocta* and *Actinopyga miliaris* (K. Chen et al., 2023; Guo et al., 2020; Wu et al., 2022). *A. leucoprocta* modulated the nematode protein DAF-16 (Wu et al., 2022). In all those studies, the pro-longevity effect of sea cucumbers was supposed to be mediated by antioxidant mechanisms. Bioactive peptides from the bivalves *Mytilus edulis* (MP) and *Arca subcrenata* (D2-G1S-1 and D2-G1S-2) extended lifespan in *C. elegans*, preventing accumulation of aging pigments (lipofuscin) and endogenous ROS levels, and improving the nematode healthspan, through the regulation of DAF-16 and other proteins of the IIS pathway (Shi et al., 2021; Zhou et al., 2018). Peptides of fish origin prolonged the lifespan of different animal models (H. Chen et al., 2020; S. Chen et al., 2020; Liang et al., 2010). In particular, marine collagen peptides, extracted from salmon (*Oncorhynchus keta*) skin, increased both mean and maximum lifespan in rats, ameliorating antioxidant defences and reducing the overall incidence of tumours (Liang et al., 2010). Crimson snapper scale peptides (CSSPs), from *Lutjanus erythropterus* scales, prolonged the mean lifespan by 21.2 % in male and 26.2 % in female flies, and increased antioxidant defences while inhibiting the accumulation of peroxide products (S. Chen et al., 2020). A novel peptide (P5) with antioxidant activity, purified from *Decapterus maruadsi* protein hydrolysate, increased the mean lifespan of *C. elegans* by 34.39 % (H. Chen et al., 2020).

Four sterols isolated from mussels (*Mytilidae*), *i.e.* cholesterol, brassicasterol, crinosterol, and 24-methylenecholesterol, extended the replicative lifespan of the yeast *S. cerevisiae*. For cholesterol, the mechanism of the anti-aging effect was explored and identified to be mediated by a protective action against oxidative stress (Sun et al., 2014).

Taken together, these studies demonstrate the potential of marine molecules — across different chemical classes and taxa — to extend lifespan and promote longevity, encouraging future research on understanding the mechanisms underlying the observed pro-longevity effects, as well as further screening to discover new promising compounds. In particular, molecules known to target the hallmarks of aging (see Chapter 3) would be valid candidates.

3. Marine bioactive compounds and the hallmarks of aging

The determinants that drive the aging process are summarized in the hallmarks of aging, defined according to three criteria, *i.e.* the age-associated occurrence, the acceleration of aging upon their increase, and the possibility to delay aging by targeting them. The latest updated version of the hallmarks includes twelve items, *i.e.* (i) genomic instability, (ii) telomere attrition, (iii) epigenetic alteration, (iv) loss of proteostasis, (v) disabled macroautophagy, (vi) deregulated nutrient-sensing, (vii) mitochondrial dysfunction, (viii) cellular senescence, (ix) stem cell exhaustion, (x) altered intercellular communication, (xi) chronic inflammation, and (xii) dysbiosis (López-Otín et al., 2023). Below, we summarize the main studies about marine bioactive molecules that have been shown to target one or more hallmarks of aging (Table 2; Fig. 2; Table S2). Since these mechanisms are highly interconnected with each other, a single compound may target several of them, but they are discussed here in different sections for major clarity. When relevant, we highlighted the main connections.

3.1. Genomic instability, telomere attrition and epigenetic alterations

A primary contribution to aging is given by the loss of genomic stability, caused by reduced efficiency of DNA repair and accumulation of genomic damage throughout life. Telomere shortening, observed in aged individuals of several species, also contributes to genomic instability, finally inducing apoptosis or senescence (López-Otín et al., 2023). Genomic instability is further exacerbated by several epigenetic

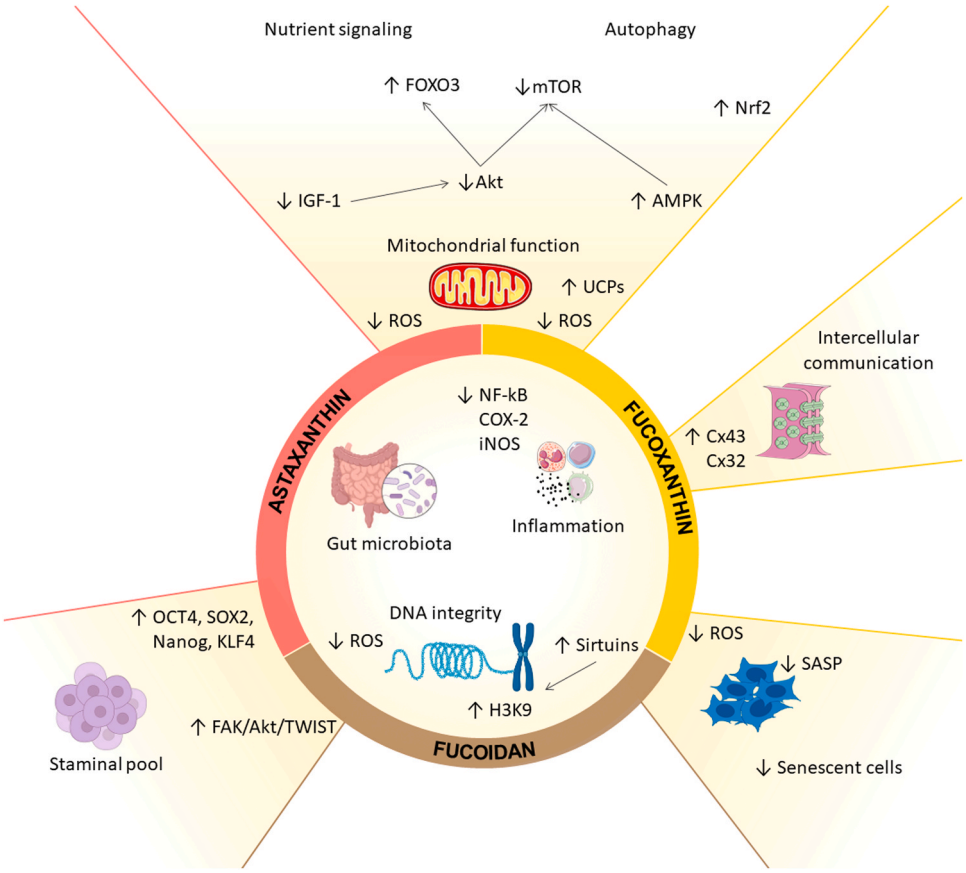

Fig. 3. *Pathways targeted by the three marine compounds displaying the major anti-aging effects: fucoxanthin, astaxanthin and fucoidan.* The diagram illustrates the principal cellular and molecular pathways modulated by these compounds. All three molecules modulate the gut microbiota, reduce inflammation by downregulating NF-κB, iNOS and COX-2, and promote DNA integrity by directly neutralizing ROS (astaxanthin), activating sirtuins (fucoxanthin, fucoidan) and increasing H3K9 (fucoidan). Astaxanthin and fucoxanthin improve mitochondrial function through a direct antioxidant effect on mitochondria (astaxanthin) and UCPs upregulation (fucoxanthin); these two molecules also modulate nutrient signaling and promote autophagy: astaxanthin inhibits IGF-1/Akt, which in turn upregulate FOXO3 and inhibits mTOR; fucoxanthin upregulates AMPK, with consequent downregulation of mTOR, and activates Nrf2-mediated autophagy. Fucoidan and fucoxanthin reduce senescent cells and SASP. Astaxanthin and fucoidan protect the staminal pool through upregulation of OCT4, SOX2, Nanog and KLF4 genes (astaxanthin) and the FAK/Akt/TWIST pathway (fucoidan). Fucoxanthin also improve intercellular communication through upregulation of Cx43 and Cx32. Only the most relevant and experimentally validated signaling routes are shown. This schematic highlights the multitarget nature of these marine bioactive compounds and their ability to modulate key processes associated with aging and longevity.

alterations associated with aging (*e.g.* altered DNA methylation patterns, histones modifications, and chromatin remodeling), which promote chromatin decondensation and enhance DNA exposure to damaging agents. Moreover, age-related epigenetic modifications — including changes in non-coding RNAs and reactivation of retrotransposons — lead to altered gene expression, thereby compromising cellular homeostasis and functions.

Genomic integrity is regulated by essential proteins (*e.g.* DNA repair enzymes and sirtuins), some of which are known to be targeted by marine-derived compounds (Table 2). Sirtuins, which induce chromatin condensation through histone deacetylation and preserve genome integrity, are of great interest for longevity, as demonstrated by several evidence, since their overexpression was shown to extend yeast, *C. elegans*, *D. melanogaster* and mouse lifespan (L. Zhao et al., 2020). The activation of Sirt1 has been reported from various sources: crude extracts of marine microorganisms such as *Micromonospora fluostatini* and *Bacillus licheniformis*, which are associated with the sponge *Scopalina hapalia* (Hassane et al., 2020); the marine compound C3, a derivative of xyloallenoide A, isolated from the mangrove fungus *Xylaria* sp. (J. Yang et al., 2023); peptides extracted from the bivalve *Mytilus edulis* (Zhou et al., 2014); and fucoxanthin (Chang et al., 2018). The algal polysaccharide fucoidan, whose role in extending lifespan was discussed above, was identified as an activator of different members of the sirtuin deacetylase family, *i.e.* Sirt1 (Yu et al., 2020, 2017; Zheng et al., 2018), Sirt3 (T. Wang et al., 2016), and Sirt6 (Rahnasto-Rilla et al., 2017), and enhances DNA repair (L. Zhang et al., 2022). Fucoidan was also able to significantly increase histone H3K9 deacetylation *in vitro* (Rahnasto-Rilla et al., 2017), which shows important links with longevity. Indeed, the deacetylation of histone H3K9 is mediated by Sirt6, whose loss induces telomere dysfunction, cellular senescence, reduced lifespan and premature aging (Kawahara et al., 2009). Several marine-derived modulators of histone modification have been identified, but so far, the main focus has been on discovering histone deacetylase inhibitors (Conte et al., 2021), which hold anti-cancer potential, but may induce chromatin relaxation. Besides fucoidan, only malformin A_1 (to the best of our knowledge), a cyclic pentapeptide isolated from the marine fungus *Aspergillus tubingensis*, was found to revert specific age-related histone modifications, by inducing an increase in the levels of H3K9 trimethylated form (H3K9me3) and H4K16 acetylated form (H4K16ac) (Notarte et al., 2017), which are usually reduced in aged people (Yi and Kim, 2020), encouraging future studies on a potential effect of malformin A_1 on aging and life extension. Since an altered distribution of heterochromatin may lead to an altered expression of retroelements, marine substances that prevent alterations of histone modifications could also be considered as potential candidates to prevent age-related activation of retroelements.

Other marine molecules, *e.g.* thiaplidiaquinones, spongolactams and cembranolide diterpene (extracted from ascidian, sponge, and coral species, respectively), have been shown to inhibit the activity of farnesyl transferase (Cadelis et al., 2017; Coval et al., 1996; Mori et al., 2007), responsible for the post-translational modification (*i.e.* farnesylation) of proteins. Permanent farnesylation of the inner nuclear membrane proteins, typical of progeria syndromes, causes changes in the nuclear morphology and promotes genomic instability (Glynn and Glover, 2005). Thus, farnesyl transferase inhibitors extend healthspan and lifespan in mice and human progeria models (Gordon et al., 2014), including the first approved drug against Hutchinson-Gilford progeria syndrome (Dhillon, 2021).

The carotenoid astaxanthin might have a direct protective role on DNA due to its well-known antioxidant properties and its recently demonstrated DNA binding ability (Sudharshan and Dyavaiah, 2021). In DNA repair-deficient mutants of *S. cerevisiae*, astaxanthin decreased the accumulation of mutations and DNA damage under oxidative stress (while enhancing the yeast longevity, as previously mentioned – see Paragraph 2) (Sudharshan and Dyavaiah, 2021). A reduction of particulate matter-induced DNA damage was also observed in human keratinocytes treated with the compound 3-Bromo-4,5-dihydroxybenzalde hyde (3-BDB), derived from the red algae *Rhodomela confervoides*, *Polysiphonia morrowii*, and *Polysiphonia urceolata* (Zhen et al., 2023).

A further target to delay the aging process by directly influencing genomic instability is the activity of telomerase, which preserves telomere erosion. Pharmacological activation of telomerase has been proposed as a promising strategy to modulate healthspan and longevity (Boccardi and Paolisso, 2014). Although several natural compounds are known to act as telomerase activators and are under investigation to attenuate age and age-related diseases (Fragkiadaki et al., 2022), only one of marine origin was described to re-activate telomerase, *i.e.* the above-mentioned xyloallenoide A derivative C3, specifically after an inhibition observed in senescence-induced endothelial progenitor cells (J. Yang et al., 2023). A study on marine sponges reported high telomerase activity in somatic cells (Koziol et al., 1998), but interestingly, only molecules with telomerase inhibitory activity have been extracted from sponges to date (Park et al., 2007; Warabi et al., 2005, 2003).

As a final insight into these hallmarks, the reactivation of retrotransposable elements seems to be a key mechanism of aging, although it remains less explored as a pharmacological target. Evidence demonstrated that aging can be delayed by nucleoside reverse-transcriptase inhibitors (NRTI), anti-viral drugs that are shown to inhibit or attenuate retrotransposition (Brochard et al., 2023). Although, to the best of our knowledge, no marine compound has been tested for anti-retrotransposon activity, many are known for their anti-viral properties (Parmar et al., 2023). The research of marine anti-viral compounds with the ability to inhibit transposition would be a novel and relevant field.

3.2. Loss of proteostasis and disabled macroautophagy

The disruption of protein homeostasis, with progressive accumulation of misfolded or damaged protein, has long been recognized as one of the main features of aging. More recently, the lack of efficient macroautophagy of waste materials, including not only proteins but also other macromolecules and entire organelles, was introduced in the hallmarks list (López-Otín et al., 2023). The impairment of autophagic clearance leads to accumulation of defective products that contribute to cellular impairment and death, with consequences on inflammatory state, tissue homeostasis and, ultimately, lifespan (Aman et al., 2021). Increasing evidence in model organisms suggests that restoring autophagy has a pro-longevity effect (Aman et al., 2021; Kaushik et al., 2021; Madeo et al., 2010). Thus, interventions that target pathways involved in proteostasis and autophagic processes are promising strategies to decelerate the aging progression. Valid targets, among the others, were shown to be the proteasome activation (Chondrogianni et al., 2015), proteins related to the unfolded protein response (UPR) (Wodrich et al., 2022), such as the eukaryotic translation initiation factor 2α (eIF2α) and the chaperon heat shock protein 70 (HSP70), as well as the transcription factor EB (TFEB), a master regulator of autophagy and lysosome biogenesis genes (Abokyi et al., 2023). A key protein in aging is the mechanistic Target of Rapamycin Complex-1 (mTORC1) kinase, a negative modulator of autophagy; mTORC1 inhibitors (among which the immunosuppressant drug rapamycin) were shown to promote longevity in several model organisms (Mannick and Lamming, 2023). Moreover, mTORC1 activation is regulated by an SLC transporter, namely SLC38A9 (Wyant et al., 2017). Due to its function in sensing amino acid sufficiency, SLC38A9 has been defi ned as a transceptor, *i.e.*, a transporter with a receptor function, and a link with autophagy has also been proven (Wyant et al., 2017). Thus, it is not trivial to expect that SLC38A9 could be listed among the targets of marine compounds modulating autophagic processes. The AMP-activated protein kinase (AMPK), which is a negative regulator of mTORC1, is also of interest as a pro-longevity intervention targeting autophagic processes (Salminen and Kaarniranta, 2012). Due to its widely studied role in mediating the cellular response to caloric restriction, molecules targeting AMPK will be discussed more in depth in the next section (see Paragraph 3.3).

A considerable number of marine compounds are known to modulate autophagic processes (Table 2; Figs. 1–2). A comprehensive review published in 2020 (Dyshlovoy, 2020) identified 16 validated activators of autophagy among marine compounds: fascaplysin, isofistularin-3, coibamide A, apratoxin A, ikarugamycin, ergosterol peroxide, stelletin B, yessotoxins, luminacin, fucoxanthin, C-phycocyanin, 2-alkylaminomethyl derivatives of jaspine B, cromomycin A2, psammaplin A, ilimaquinone, and petromurin C. In recent years, the number of suggested autophagic activators has further increased, including laxaphycins (Alvarinõ et al., 2020), astaxanthin (Fu et al., 2021), clionamines (Persaud et al., 2022), nigrosporins B (J. Zhang et al., 2022), and piericidin analogue S14 (PA-S14) (Liu et al., 2022). The mechanistic target of such effect, where described, is in most cases the AMPK/mTOR axis (Table 2) (Alvarinõ et al., 2020; Fu et al., 2021; Kumar et al., 2015; Liao et al., 2016; Liu et al., 2022; Qu et al., 2022; Wang et al., 2017; R. Wang et al., 2016; Wu et al., 2018). Inhibition of the mTOR signaling was also observed by other marine products (*i.e.* halichondramide, flaccidoxide-13-acetate, hamacanthins, and the extract of the nudibranch *Phyllidia varicosa*), not specifically tested for autophagy modulation (Bae et al., 2013; Kim et al., 2013; Ruiz-Torres et al., 2018; Wu et al., 2020). A molecular docking experiment identified 137 candidate mTOR inhibitors of marine origin, highlighting the potential of marine compounds to target the *disabled macroautophagy* hallmark (Ruiz-Torres et al., 2018).

To give some mechanistic details (Table 2), ikarugamycin (see Chapter 2), selected through a screening of TFEB agonists that induce autophagolysosome activity, promotes autophagy *in vitro* through mobilization of Ca^{2+} from the endoplasmic reticulum (ER), followed by activation of TFEB and AMPK, and inhibition of mTORC1 activity (Wang et al., 2017). Yessotoxins (polyether compounds produced by dinoflagellate marine microalgae) induce inhibition of mTORC1 in mouse brain tumor cells (Korsnes et al., 2016) and in human glioma cells, where they were also able to enhance UPR-related gene expression and the phosphorylated active form of eIF2α, as a consequence of ER-stress (Rubiolo et al., 2014). The activation of proteostatic systems (proteasomal activity, the chaperons CLU, HSP27, HSP70) and autophagy-related proteins was observed in human cells after exposure to the extract SA223-S2BM, purified from the marine bacterium *Salinispora arenicola*, a soft coral symbiont; the proteasome activation by SA223-S2BM extract was confirmed in *D. melanogaster* flies, although without effects on lifespan and healthspan (Louka et al., 2021). The piericidin analogue S14 (PA-S14), isolated from a marine *Streptomyces* strain, stimulates autophagosome maturation and autophagic flux *in vitro* and in mice through the binding and activation of the liver kinase B1 (LK-B1, a key regulator of energy metabolism) and subsequent AMPK activation

(Liu et al., 2022). Effects on mitochondria and cellular senescence were also observed (see Paragraphs 3.3 and 3.4). A mechanism involving a different pathway was instead ascribed to fucoxanthin, whose activating effect on autophagy, observed both *in vitro* and in mice brain after injury, was mediated by the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2), a key transcription factor of antioxidant system and recently described as a regulator of macroautophagy genes (Zhang et al., 2017). This opens a new perspective for many antioxidant marine molecules as autophagy-targeting modulators of aging.

3.3. Deregulated nutrient-sensing and mitochondrial dysfunction

The regulation of nutrient-sensing pathways plays a crucial role in aging (Tomtheelnganbee et al., 2022). Health benefits and lifespan extension may be achieved by caloric restriction in several species, from nematodes to mice, as well as by genetic alterations that diminish the activity of the nutrient signaling pathways (Dorling et al., 2020; Fontana et al., 2010). Moreover, pharmacological interventions that mimic the effects of dietary restriction (*e.g.* the administration of resveratrol, rapamycin or metformin) demonstrated the ability to promote longevity in animal models (Lee and Min, 2013). The key proteins involved in nutrient sensing include the insulin-like growth factor 1 (IGF1) and other members of the IIS, AMPK, mTORC1, and sirtuins. Such nutrient sensors can be targeted for anti-aging interventions, in particular inhibiting the IIS and mTORC1, and activating AMPK and Sirt (López-Otín et al., 2023). Recently, the inhibition of the anaplastic lymphoma kinase (ALK) has emerged as promising for extending healthy lifespan by reducing the IIS signaling (Woodling et al., 2020). The same pathways have a great importance also in mitochondrial physiology and aging. Indeed, age-dependent changes in mitochondrial function (including impaired bioenergetics, reduced biogenesis and inhibition of mitophagy) can be mitigated by the same interventions that target nutrient sensing (Amorim et al., 2022). Moreover, the nutrient-sensing network and the mitochondrial processes are closely interconnected to autophagic pathways, as also underlined by the involvement of mTORC1 and AMPK (see Paragraph 3.2).

A few marine compounds have been shown to exert an inhibitory activity on the IIS pathway (Table 2). Laminarin, from brown algae, decreased the expression of the IGF1 receptor (IGF1R) and downstream proteins (PI3K, PY99, Akt, MAPK, IRS-1) (Park et al., 2012). Interestingly, laminarin-rich extract supplementation increases the expression of SLC2A8/GLUT8 in the duodenum, SLC2A2/GLUT2, SLC2A7/GLUT7, SLC15A1/PEPT1 and FABP2 in the jejunum and SLC16A1/MCT1 in the colon (Rattigan et al., 2020), improving intestinal health. This may be related to the overall nutrient sensing mechanism in aging. Compounds derived from the sponge *Cribrochalina vasculum* decreased IGF1R phosphorylation and inhibited downstream signaling in tumor cells by binding to the kinase domain of IGF1R; however, such effects were not seen in normal fibroblasts (Zovko et al., 2016). A potent inhibitory activity on IGF1R and ALK was displayed by compounds from the sponge *Dactylospongia metachromia* (sesquiterpene aminoquinones, sesquiterpene benzoxazoles and 18-hydroxy-5-epi-hyrtiophenol) (Daletos et al., 2014) and by astrogorgols from the gorgonian *Astrogorgia sp.* (Lai et al., 2011). The carotenoid astaxanthin, while activating autophagy through mTORC1 inhibition (see Paragraph 3.2), was shown to inhibit IGF1 in a mouse model of accelerated aging (SAMP8) (Fu et al., 2023). Several pieces of evidence demonstrated its ability to ameliorate mitochondrial dysfunction through a direct action *in vitro* and *in vivo,* in mice and geriatric dogs, mainly by maintaining mitochondrial integrity and membrane potential, increasing mitochondrial content and activity, and reducing mitochondrial ROS production and depolarization (Kim and Kim, 2018). In the *C. elegans* model, GP polysaccharide and marine peptides (SCP, MP, D2-G1S) have been shown to increase lifespan through the IIS pathway, *e.g.* regulating DAF-2/IGF1R, AGE-1/PI3K, and DAF-16/FOXO, a downstream protein of the IIS pathway (see Chapter 2).

AMPK activation, both direct and indirect, has an interesting pro-longevity potential, due to the central role of AMPK in cellular homeostasis, so that some widely studied candidates for lifespan/healthspan extension, *i.e.* resveratrol and metformin, are AMPK activators (J. Kim et al., 2016). A direct and high AMPK activation was observed for the methanolic extract of the sponge *Callyspongia samarensis*, which also appeared devoid of acute oral toxicity in mice (Resuello et al., 2020). Another marine AMPK ligand and potent activator, both *in vitro* and in mouse models, is candidusin A, isolated from the coral symbiont *Aspergillus candidus*, also known for lipid-lowering, anti-apoptotic and neuroprotective activities (J. Chen et al., 2023). Aglycon of rhizochalin, a sphingolipid-like compound isolated from the sponge *Rhizochalina incrustata*, activates AMPK phosphorylation and inhibits mTOR pathway in cancer cells *in vitro*, showing also pro-apoptotic properties (Khanal et al., 2011). The algal carotenoid fucoxanthin and the PPARα/γ ligand dihydrotrichodimerol, isolated from the marine fungus *Acremonium citrinum*, are both indirect AMPK activators, inducing AMPK phosphorylation through the upregulation of Sirt1; as a consequence on nutrient metabolism, a reduction of lipid accumulation was observed *in vitro* for both molecules, and in a mouse model for dihydrotrichodimerol (Chang et al., 2018; Liu et al., 2023a, 2023b). Polyoxygenated steroids from the sponge *Clathria gombawuiensis* (gombasterols A–F and clathriol), and 6, 8-di-O-acetylmalyngamide 2, isolated from the marine cyanobacterium *Moorea producens*, were shown to activate AMPK, with an improvement of glucose uptake in cultured muscular cells (Sueyoshi et al., 2017; Woo et al., 2017).

Fascaplysin, a marine alkaloid initially isolated as a red pigment from the sponge *Fascaplysinopsis reticulata*, is a known inhibitor of the cyclin-dependent kinase CDK4 and widely studied for its anti-cancer, anti-angiogenetic and pro-apoptotic properties (Wang et al., 2023). Interestingly, fascaplysin causes a potent P-glycoprotein (P-gp) induction, which is one of the most recent strategies for increasing the clearance of β-amyloid plaques in Alzheimer's disease (AD) (Manda et al., 2016), further supporting its potential in aging (see Paragraph 4.1). In addition, several pieces of evidence suggest its possible effect in aging pathways, and it was claimed that it can act in a similar way to rapamycin (Oh et al., 2017). Besides being a validated activator of autophagy (see Paragraph 3.2), fascaplysin increased phosphorylation of AMPK and its downstream target, the acetyl-CoA carboxylase (ACC) (Oh et al., 2017), involved in lipid metabolism, suggesting a potential to inhibit the nutrient-sensing network. Further, fascaplysin was shown to activate PPARγ-coactivator-1α (PGC-1α) (Oh et al., 2017), a key inducer of mitochondrial biogenesis. However, its activity was also associated with mitochondrial depolarization and severe ATP depletion in cancer cells (Oh et al., 2017); thus, its mechanism of action and toxicity need to be further investigated. Conversely, the upregulation of AMPK and PGC-1α was shown to mediate an increased mitochondrial function observed in mice after treatment with sea cucumber peptides (SCP-1 and SCP-2), which also improved the muscular performance of the animals (Q. Wang et al., 2021).

Mitochondrial biogenesis was also promoted by the piericidin analogue PA-S14, known as a LK-B1 ligand, AMPK activator and autophagy inducer (see Paragraph 3.2), both in a human kidney cell line and in mouse models (Liu et al., 2022). Conversely to other piericidins, which are known to be potent inhibitors of mitochondrial complex I (Zhou and Fenical, 2016), PA-S14 showed no inhibitory effect on complex I and low toxicity (Liu et al., 2022). An effect on mitochondrial functions was also observed by acyclic laxaphycins, lipopeptides derived from the marine cyanobacteria *Anabaena torulosa*, which reduced mitochondrial membrane potential, ATP levels and ROS production in human neuroblastoma cells, with subsequent AMPK phosphorylation, mTORC inhibition and stimulation of autophagic flux (see Paragraph 3.2) (Alvarinõ et al., 2020). Such compounds are believed to act through a mechanism similar to that of metformin, a known antidiabetic drug with anti-aging properties that induces AMPK activation by inhibition of complex I of the mitochondrial respiratory chain and subsequent

reduction of ATP levels (J. Kim et al., 2016). Another indirect activator of AMPK that acts through a reduction of ATP levels is the marine-derived macrolactone mandelalide A, from the tunicate *Lissoclinum ascidian* (Mattos et al., 2022). Mandelalides are direct inhibitors of mitochondrial ATP synthase, thus activating AMPK in response to depletion of cellular ATP (Mattos et al., 2022). Lastly, mussel's oligopeptides ameliorate the loss of mitochondrial membrane potential induced by H_2O_2 in human fibroblast cells, probably through modulation of Sirt1 (see Paragraph 3.1) (Zhou et al., 2014), and a similar effect was observed in keratinocytes for the algal compound 3-BDB (Zhen et al., 2023).

As stated in the introduction, the flux of molecules with potential pro-longevity effects must be guaranteed by membrane transporters. In the context of mitochondrial energetics, a crucial role is played by the ATP/ADP carrier, the uncoupling protein (UCP), and the Carnitine/AcylCarnitine (CAC) carrier, involved in ATP synthesis, thermogenesis, and oxidation of fatty acids, respectively. Therefore, compounds able to regulate the expression and function of these transporters may also be relevant in triggering bioenergetic processes or in managing mitochondrial dysfunction typical of aged cells. Interestingly, fucoxanthin was shown to induce the expression of UCP-1, −2 and −3 in the visceral adipose tissue of obese mice (Woo et al., 2009), a possible explanation of its known hypolipidemic effect. Moreover, several data are available on the effect of some antioxidant compounds on the CAC functionality due to the specific interaction with a couple of Cys residues uniquely present in this transporter but not in other mitochondrial carriers (Tonazzi et al., 2021). These findings highlight the crucial role of CAC as a sensor in redox stress with potential consequences on mitochondrial bioenergetics in longevity. Based on this capacity, it is not trivial to hypothesize that the CAC, and hence the mitochondrial bioenergetics, could be influenced by redox-regulating marine drugs.

3.4. Cellular senescence

Cellular senescence, a permanent state of cell cycle arrest, is characterized by a peculiar phenotype, including accumulation of lysosomal content and mitochondria, loss of autophagy, enlarged nuclear size, loss of lamin B1 from the nuclear envelope, increased DNA damage, and production of the Senescence-Associated Secretory Phenotype (SASP). In the presence of a functional immune response, senescent cells are efficiently cleared by immune cells. However, in aged people, senescent cells accumulate in the tissues, promoting an inflammatory status and an environment favourable to the development of pathologies and accelerated aging (Van Deursen, 2014). The pharmacological elimination of senescent cells through the use of senolytics (*i.e.* compounds which selectively kill senescent cells) has emerged as a promising approach to ameliorate the aging phenotype. Senolytic strategies include the inhibition of anti-apoptotic/pro-survival networks and induction of autophagy (*e.g.* by targeting Bcl-2 family members, caspases, p53-p16-p21-FoxO4 pathway, Hsp90 chaperones, USP7 peptidase, the PI3K-AKT axis, Src kinase, the ephrin dependence receptor signaling, mTORC1) (Gasek et al., 2021). Despite a growing number of pre-clinical studies, only a few senolytics have a demonstrated effect in humans (Gasek et al., 2021), leaving a vast space for the discovery of novel senolytic compounds.

A recent study identified promising marine phycocompounds as senotherapeutics through an *in silico* screening of 1202 algae-derived compounds (Salekeen et al., 2022). Preliminary findings suggest that debromoaplysinol, a toxic agent from *Laurencia tristicha*, along with dichotenone-A from *Dictyota dichotoma* and C15 acetogenin from *Laurencia glandulifera*, could inhibit the anti-apoptotic Bcl-XL protein. Additionally, ketones from *Dictyota bartayresiana* and laurefurenyne A from *Laurencia sp.* were found to block the hypoxia-inducible factor 1α (HIF1α) transcription factor, a key regulator of senescence and senolysis-associated metabolic networks. Moreover, two enantiomers of a xenicadiene derivative from *Dilophus fasciola*, along with lembyne-A, were identified as the most promising molecules for inhibiting Foxo4, a key transcription factor downstream of the AMPK-mTOR-Sirt1 signaling pathway (Salekeen et al., 2022). Despite this, only a few marine compounds have been experimentally tested for their senolytic properties.

The marine molecule PA-S14 (see Paragraphs 3.2 and 3.3) revealed senolytic properties *in vivo*, by reducing renal cell senescence in a mouse model of acute kidney injury and chronic kidney disease (UIRI mice) (Liu et al., 2022). The xyloallenoide A derivative C3, previously mentioned as a Sirt1 activator (see Paragraphs 3.1), reduced angiotensin II-induced senescence of human endothelial progenitor cells *in vitro* through Sirt1 overexpression (J. Yang et al., 2023), highlighting a potential role in the treatment of the endothelial dysfunction, of high interest in the elderly. Marine collagen peptides from fish skin and fish cartilage reduced cellular senescence in human articular chondrocytes (Bourdon et al., 2021) (Table 2; Fig. 1).

A recent study highlighted the role of fucoidans as potential senotherapeutics, specifically reducing markers of cellular senescence and SASP in senescent mouse and human cells, and in kidney and lung of naturally aged mice. As stated in Chapters 2 and 3.1, fucoidans can improve age-related phenotypes and extend the healthspan of a progeria mouse model by enhancing DNA repair mechanisms through the modulation of SIRT6 activity (L. Zhang et al., 2022).

Other marine-derived molecules were found to have a preventive role on senescence occurrence *in vitro* and/or *in vivo*, since the pretreatment with such compounds reduced the proportion of senescence-induced cells (Table 2; Fig. 1). Among them, fucoxanthin action was mediated by its strong antioxidant potential, as observed in retinal pigment epithelium cells *in vitro* and in an *in vivo* model of age-related macular degeneration disease, which opens important implications for the treatment of ocular neurodegenerative disease (Chen et al., 2021). 3-BDB, from red algae, prevented the accumulation of senescent keratinocytes *in vitro* and in mouse skin, while alleviating ROS levels, DNA damage, mitochondrial dysfunction and inflammation (see Paragraphs 3.1 and 3.3) (Zhen et al., 2023). A preventive effect on senescence by porphyran, GP polysaccharides, and mussel's oligopeptides was observed in embryonic lung cells or lung fibroblast (Wang et al., 2022b; Z. Zhang et al., 2018; Zhou et al., 2014). This evidence shows that the protective action of marine molecules towards senescence may be carried out on specific cell types and tissues, and this may have interesting implications in the use of specific compounds for the prevention of age-related decline of organ function and consequent diseases.

Notably, the senescence of mesenchymal stem cells (MSCs) was reduced by the polysaccharide fucoidan and C-phycocyanin (C-PC), a photosynthetic pigment from the cyanobacterium *Spirulina platensis*, with important implications on the preservation of the staminal compartment (see Paragraph 3.5) (Lee et al., 2018; L. Zhang et al., 2022).

3.5. Stem cell exhaustion

Adult stem cells are undifferentiated cells, which represent a long-term reservoir of cells characterised by self-renewal and multilineage differentiation potential. As we age, adult stem cells gradually lose these properties, accumulating damage and contributing to a progressive exhaustion of their reserves, ultimately leading to impaired tissue fitness and functionality and reduced regenerative capacity upon injury (Ren et al., 2017). Stem cells are particularly exposed to sources of DNA damage (Vitale et al., 2017), but can rely on a robust DNA damage response and checkpoints, which act as a quality control, safeguarding stem cells' genomic stability and regulating their functional state (Sperka et al., 2012). However, during aging, the persistent demands of homeostatic maintenance inadvertently weaken these mechanisms, significantly compromising the genetic stability of stem cells (Pazhanisamy, 2009). Thus, DNA damage accrual limits the functionality of stem cells and contributes to the decline of tissue renewal

capacity (Rossi et al., 2007). Similarly, mitochondrial progressive dysfunctions can influence stem cells' fate. Increased mitochondrial alterations and ROS production in neural stem cells correlate with a higher predisposition to differentiate towards the astrocytic lineage, determining neurodegeneration and brain injuries (Wang et al., 2011). Accordingly, marine-derived molecules that mitigate DNA damage and mitochondrial dysfunction – topics thoroughly explored in Paragraphs 3.1 and 3.3 – could indirectly ameliorate stem cell exhaustion. Indeed, by improving genomic stability and mitochondrial function, these compounds might act as protective agents, supporting long-term stem cell maintenance.

Understanding the diverse signaling pathways in adult stem cells opens new avenues for developing targeted therapies against age-related disorders, such as those involving the use of marine molecules. Many of them exploit antioxidant strategies by scavenging free radicals and altering peroxide chain reactions. Indeed, ROS neutralization is known to reduce DNA damage, mutations, and chromosomal instability, which contribute to the functional decline of stem cells. Moreover, excessive ROS accumulation can drive premature differentiation and accelerate stem cell exhaustion (Liao et al., 2019; Papa et al., 2019). Therefore, protecting stem cells from oxidative stress may help preserve their pool over time and prevent tissue dysfunction.

Among carotenoids, astaxanthin has the most potent antioxidant activity, which has been demonstrated to improve bone marrow cell injury after radiation and improve haematopoietic self-renewal in mice (Xue et al., 2017). Recent evidence also shows that astaxanthin reduces ROS accumulation and mitochondrial superoxide levels in osteoblasts by activating the Nrf2 signaling pathway, thereby counteracting glucocorticoid-induced oxidative stress, mitochondrial dysfunction, and impaired osteogenic differentiation (Wang et al., 2024). Currently, it has been widely accepted that astaxanthin has a protective role in bone, by preventing age-related diseases like osteoporosis and osteoarthritis (see Paragraph 4.5) (Valenti et al., 2020). Another line of *in vitro* studies showed an effect of astaxanthin in the differentiation of neural stem cells towards neurons via FOXO3 and antioxidant pathways, which fuel glia formation together with chronic inflammation. Indeed, astaxanthin was defined as a putative "geroneuroprotector", since it plays a role in preventing brain aging (Sorrenti et al., 2020). Moreover, the use of astaxanthin induced upregulation of proliferation-related transcription factors (Rex1, CDK1 and CDK2), together with stemness genes (OCT4, SOX2, Nanog and KLF4), thus improving the stemness and proliferation capacity of neural stem cells (Kim et al., 2010b) (Table 2; Figs. 2–3).

Another potent marine antioxidant is the carotenoid fucoxanthin, which is known to decrease ROS levels and DNA damage (see Paragraph 3.1) while restoring mitochondrial membrane potential and (see Paragraph 3.3) suppressing apoptosis in human keratinocytes (Zheng et al., 2013). In an *in vitro* cellular model of mesenchymal stromal cells, fucoxanthin demonstrated a cytoprotective, pro-survival and proliferative activity under oxidative stress conditions (Suwanmanee et al., 2023) (Table 2; Figs. 2–3).

As well as astaxanthin and fucoxanthin, the algal polysaccharides fucoidans exert an antioxidant activity with a protective effect on senescence-induced inhibition of proliferation of MSCs *in vitro* (Lee et al., 2018). In this scenario, fucoidans significantly reduced senescence markers (see Paragraph 3.4), while enhancing cell proliferation by activating FAK-Akt-TWIST signaling pathway (Lee et al., 2016a, 2016b). which helps counteract cellular aging (Table 2; Figs. 2–3). Other than its effect on proliferation, fucoidans have been known for their pro-osteogenic properties, demonstrated in human MSCs, where the increase of osteogenic genes, such as ALP, runt-related transcription factor 2 (RUNX2), type 1 collagen alpha (COL1a) and osteocalcin have been observed (B. S. Kim et al., 2015).

Among the micro-algae, spirulina has gained much attention for its antioxidant, anti-inflammatory, and immunomodulatory effects, making it a potential candidate as a natural compound to be used in functional foods, pharmaceuticals and nutraceuticals. In a recent study, young rats were fed for 30 days with a spirulina-rich diet, which reduced the negative impact of LPS-induced neuroinflammation in hippocampal neural progenitor cells, compared to controls, suggesting that spirulina could protect stem cells from acute insults (Bachstetter et al., 2010). However, the main effect of spirulina is provided by one of its key bioactive molecules, C-PC (Liu et al., 2016). As mentioned in 3.4, treatments with C-PC have demonstrated an active role in ameliorating senescence in bone marrow-derived MSCs via PI3K/AKT/mTOR signaling pathway, both *in vitro* and in aging rats (Liu et al., 2023a, 2023b) (Table 2).

Providing stem cell health is also crucial to maintain the structural integrity of tissues, given that as we age, the reduced stem cell activity, together with oxidative stress and impaired cell signaling, leads to poor regenerative potential. Marine collagen, derived from marine organisms like fish, is gaining attention for its potential to counteract these effects by promoting cellular repair and enhancing extracellular matrix (ECM) health through reducing matrix metalloproteinase 1 (MMP1) levels (Bourdon et al., 2021) (Table 2). As a consequence, marine collagen from fish skin is widely used as a scaffold biomaterial in the tissue regenerative industry, together with other marine polymers, such as fucoidans and chitosan from squid pens (Carvalho et al., 2023; Lim et al., 2019). Similarly, hydrogels based on alginate, a polysaccharide extracted from brown algae, have emerged as a promising biopolymer for cardiac regeneration, demonstrating significant potential in both preclinical models (Saludas et al., 2017) and clinical trials (Mann et al., 2016). Their unique biocompatibility and advantageous physical properties – *i.e.* hydrophilicity that enhances compatibility with body fluids, gelling behaviour for easier manipulation, and porosity that facilitates cell infiltration and nutrient transport – make them suitable for several applications, including drug delivery or tissue scaffold systems (Cattelan et al., 2020).

3.6. Altered intercellular communication

Precise intercellular communication among cells, tissues, and organs is essential for maintaining the homeostasis of a healthy organism. Its disruption has been linked to aging and the onset of various age-related diseases (López-Otín et al., 2013; Ribeiro-Rodrigues et al., 2022). When discussing altered intercellular communication during aging, four primary mechanisms are deregulated: direct cell-to-cell communication through gap junctions, the SASP, hormonal regulation, and ECM alterations.

Gap junctions are intercellular channels facilitating the exchange of second messengers, ions, small metabolites, and other molecules between adjacent cells. These channels have a key role in pathological condition onset, regulating Ca^{2+} homeostasis, ROS detoxication and membrane depolarisation (Belousov et al., 2017; Orellana et al., 2012). Gap junction channels are formed by docking two hexameric hemichannels, each consisting of six subunits, belonging to the connexin (Cx) protein family, with Connexin43 (Cx43) being the most widely expressed and studied (Retamal et al., 2007; Yeager and Nicholson, 1996). It has been described that the aging process is associated with a decrease in Cx43 protein levels in cardiomyocytes, osteocytes and hematopoietic stem cells (HSC) (Davis et al., 2017; Ishikawa et al., 2012; Michela et al., 2015). Research on marine-derived compounds and their effects on gap junctions remains limited, representing an emerging frontier in biomedical studies. Among these compounds, the carotenoid fucoxanthin has shown promising activity. Fucoxanthin significantly enhanced gap junctional intercellular communication (GJIC) *in vitro*, with a notable increase in protein and mRNA expression levels of connexins Cx43 and Cx32, key components of functional gap junctions (Liu et al., 2009) (Table 2; Fig. 3). Cnidarian polyps and jellyfish are emerging as valuable sources of bioactive compounds with physiological relevance. In particular, an extract derived from the scyphozoan *Cotylorhiza tuberculata* was investigated for its effects on GJIC functionality. Remarkably, the extract exhibited a significant time- and

dose-dependent enhancement of GJIC *in vitro*, with its effects becoming increasingly pronounced at varying concentrations. This highlights the potential of jellyfish-derived compounds in modulating cellular communication pathways (Leone et al., 2013).

SASP is a complex secretory phenotype through which senescent cells influence their surrounding environment (see Paragraph 3.4). The SASP is enriched in pro-inflammatory cytokines like interleukin-1β (IL-1β), IL-6, tumour necrosis factor α (TNF-α), and transforming growth factor β (TGF-β), often delivered by extracellular vesicles (EVs), which are membrane-encapsulated vesicles secreted by cells into the extracellular space, capable of travelling throughout the organism (Doyle and Wang, 2019; Kalluri and LeBleu, 2020). Studies have shown that EVs secreted by senescent cells are functionally active in other cells and are now recognized as part of the SASP, significantly contributing to the cellular and tissue alterations observed during aging (Alibhai et al., 2020). Notably, EVs derived from senescent cells display distinct profiles in proteins and miRNAs compared to those from healthy cells, influencing the activity of surrounding cells. For instance, senescent EVs exhibit elevated IL-1β levels, impacting inflammatory signaling in recipient cells (Gomes De Andrade et al., 2018). The SASP phenotype enhances the senescent milieu in an autocrine manner, often inducing senescence in nearby cells through the bystander effect (Nelson et al., 2012). Marine molecules that target cellular senescence (see Paragraph 3.4) have the consequent effect of modulating the release of inflammatory cytokines in the surrounding tissue. Similarly, the secretion of pro-inflammatory SASP molecules may be inhibited by anti-inflammatory marine compounds, which will be extensively covered in the following Paragraph (see Paragraph 3.7). To cite a few, numerous algal metabolites have demonstrated anti-inflammatory mechanisms targeting pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α (Table 2); some examples are bromophenols, carotenoids, alkaloids and flavonoids. The bromophenol 3-bromo-4,5-dihydroxybenzaldehyde (3-BDB), isolated from the red alga *Polysiphonia morrow*, has been extensively documented for its broad immunomodulatory effects, particularly in inhibiting the production of IL-6, TNF-α, and IFN-γ (Kang et al., 2017). Similarly, 3-bromo-4,5-dihydroxybenzyl ether (BBDE), derived from *Polysiphonia urceolata*, has been shown to mitigate inflammatory responses in LPS-activated macrophage cells by downregulating pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Choi et al., 2018). Among carotenoids, astaxanthin has demonstrated the ability to suppress IL-6 production in an *in vitro* model of activated microglial cells (Kim et al., 2019). Furthermore, the indole alkaloid caulerpin, isolated from green algae of the *Caulerpa genus*, effectively reduced inflammatory infiltrates and pro-inflammatory cytokines, including IL-6, IL-17, IFN-γ and TNF-α, through nuclear factor kappa B (NF-κB) inhibition, while increasing the anti-inflammatory IL-10 (Lucena et al., 2018).

Hormones play a crucial role in cellular communication by acting as chemical messengers that orchestrate various physiological processes. This communication system is essential for maintaining homeostasis, coordinating growth, metabolism, and other vital functions, and its dysregulation can lead to different diseases, among which are some age-related ones (Cappola et al., 2023). Hormonal dysregulation becomes increasingly evident with advancing age. For instance, the thyrotropic axis undergoes significant changes during aging, most notably characterized by elevated serum thyroid-stimulating hormone (TSH) levels. This alteration appears to be influenced by iodine status (Bremner et al., 2012). Despite the generally low iodine concentrations in seawater, several seaweeds that thrive in shallow waters have demonstrated a remarkable capacity to concentrate iodine from their environment, positioning them as potential dietary sources to address iodine imbalances. Key examples of iodine-rich seaweeds include *Ulva lactuca, Palmaria*, and *Laminaria*, which belong to the green, red, and brown algae groups, respectively (Smyth, 2021). These marine organisms could offer a natural avenue for replenishing iodine levels and mitigating age-associated thyroid dysregulation.

Another axis that becomes dysregulated with age is the hypothalamic–pituitary–somatotropic axis, which governs the secretion of somatotropin, commonly known as growth hormone (GH). GH, in turn, stimulates the production of IGF-1, a critical mediator of growth and metabolic processes.

The age-related decline in GH levels, named *somatopause*, is well-documented. This decline begins shortly after puberty and progressively continues throughout adulthood, contributing to various physiological changes associated with aging. Reduced GH and IGF-1 levels are linked to decreased muscle mass, bone density, and metabolic efficiency, highlighting the importance of this axis in maintaining overall health during aging (Junnila et al., 2013; Laron et al., 2017).

Research on the upregulation of IGF-1 expression by marine-derived compounds is still in its early stages, but promising findings have emerged. Pyrroloquinoline quinone (PQQ), a compound produced by various marine bacteria, has enhanced IGF-1 expression and basic fibroblast growth factor (bFGF). This effect was accompanied by a significant reduction in key inflammatory cytokines, including IL-1β and TGF-β (Wang et al., 2021). Additionally, two polyphenols isolated from the edible brown alga *Ecklonia cava*, dieckol and 2,7″-phloroglucinol-6, 6′-bieckol (PHB), have demonstrated the ability to stimulate skeletal muscle growth by promoting IGF-1 expression (Kim et al., 2021).

Another key feature of altered intercellular communication during aging is the extensive disruption of the ECM (López-Otín et al., 2013), which serves not only as a structural scaffold but also as a dynamic environment that mediates interactions between cells and their surroundings. It facilitates cell-cell communication through mechanical signals without direct contact (Nahum et al., 2023). In this context, the TGF-β and NOTCH signaling pathways play crucial roles (Yi et al., 2017). TGF-β is a key regulator of the synthesis, degradation, and remodelling of the ECM. Its activity is closely linked with ECM dysregulation (Chakravarthy et al., 2018), as it promotes the synthesis of various ECM components, including collagens and fibronectin (Shah and Prajapati, 2024). Recent studies have highlighted that excessive activation of TGF-β-regulated Notch signaling occurs in liver fibrosis in rats. Additionally, inhibiting TGF-β signaling has been shown to block Notch signaling and *vice versa* (Yi et al., 2017). This confirms a complementary mechanism previously observed in other studies (Xiao et al., 2014). Marine-derived compounds have been extensively studied for their ability to modulate TGF-β activity in cancer, fibrosis, and inflammation contexts. For instance, steroidal components extracted from the Red Sea soft coral *Sarcophyton glaucum* significantly reduced TGF-β expression, alleviating fibrosis in a liver fibrosis model (Tammam et al., 2023). Similarly, hyrtiosal, an inhibitor of protein tyrosine phosphatase 1B isolated from the marine sponge *Hyrtios erectus*, was found to disrupt TGF-β/Smad2 signaling, highlighting its therapeutic potential (Sun et al., 2007). Additionally, phloroglucinol, a natural phlorotannin derived from brown algae, decreased the expression of Notch2 and Oct4 in breast cancer cells, further demonstrating the multifaceted regulatory effects of marine bioactive substances on TGF-β-associated pathways (R.-K. Kim et al., 2015). Other compounds promoting ECM health in the field of regenerative medicine, *i.e.* marine collagen, chitosan and alginate, were previously discussed in Paragraph 3.5.

In the final analysis, the intricate interplay of intercellular communication mechanisms is crucial for preserving organismal homeostasis, and its disruption contributes significantly to aging and related disorders. Despite being in the early stages of exploration, marine-derived compounds display promising therapeutic properties, from modulating SASP factors to influencing key signaling pathways, including the somatotropic and thyrotropic axes. Therefore, these bioactive agents represent an emerging and exciting strategy to target such pathways, with potential applications in spanning senescence modulation, hormonal balance restoration, and growth factor regulation.

3.7. Chronic inflammation

Inflammation is widely recognized as a central factor in the aging process (López-Otín et al., 2013). This chronic, low-grade inflammation associated with aging is often called *inflammaging* (Franceschi et al., 2000; Salvioli et al., 2013; Santoro et al., 2021). Inflammaging arises from a diminished ability to respond to various stressors and a progressive increase in antigenic load, leading to a pro-inflammatory state (Franceschi et al., 2007). Like many other organs and systems in the body, the immune system experiences senescence, a process known as immunosenescence. This results in a gradual decline in its functional efficiency and an increase in inflammation. Inflammaging does not originate solely from the primary immune cells; it also results from other hallmarks of aging, *e.g.*, mitochondrial dysfunctions, epigenetic dysregulation, and impaired autophagy, which can trigger inflammation (López-Otín et al., 2013).

This understanding allows us to consider the lifelong pro-inflammatory process as an adaptation that may have beneficial or detrimental effects. This extensive remodeling impacts nearly all aspects of the immune system, with the most significant effects observed in the adaptive immunity branch (Fulop et al., 2009). A prominent characteristic of aging in the immune system is the increased proportion of late effector and memory T cells and a concurrent decline in naïve lymphocytes (Franceschi et al., 2000; Santoro et al., 2021). Additionally, immunosenescence is characterized by a decrease in the number and frequency of B cells and an increase in myeloid and natural killer cells (Derhovanessian et al., 2008). Furthermore, aging is associated with elevated plasma levels of circulating cytokines, such as IL-1β, IL-6, and TNF-α, as well as other pro-inflammatory markers like C-reactive protein (Michaud et al., 2013). Notably, this chronic inflammatory state has been linked to the development of various age-related diseases, including cardiovascular disease, cancer, and neurodegenerative disorders (Ferrucci and Fabbri, 2018; Rea et al., 2018).

Effective interventions are essential to counteract inflammaging and promote healthy longevity. In recent years, extensive research suggests that marine-derived compounds could be promising in modulating the inflammatory processes associated with aging. Hundreds of compounds, derived from algae, sponges, and marine bacteria, exhibit potent anti-inflammatory properties (Mayer et al., 2024), including those mentioned in paragraph 3.6 for SASP mitigation, making them candidates for geroscience interventions.

Among these, the carotenoid pigment astaxanthin has demonstrated robust anti-inflammatory properties. Its ability to downregulate the activation of NF-κB, inhibit nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), and suppress the expression of pro-inflammatory cytokines underscores its potential in combating chronic inflammation associated with aging (Kohandel et al., 2022). Similarly, the phlorotannin diphlorethohydroxycarmalol (DPHC), isolated from the brown alga *Ishige okamurae*, has shown efficacy in inhibiting the nuclear translocation of NF-κB on LPS-stimulated murine macrophages. Interestingly, at higher concentrations, DPHC also reduces the expression of signal transducer and activator of transcription 5 (STAT5), suggesting its broader role in modulating inflammatory signaling pathways (Kang et al., 2015). Moreover, DPHC was revealed to promote glucose transport via the plasma membrane transporter GLUT4 in muscles (Yang et al., 2021). These results suggested a potential role in the prevention of diabetes, a pathological condition often associated with aging (see Paragraph 4.3).

Other compounds act through related mechanisms involving the suppression of inducible iNOS and pro-inflammatory mediators. Phorbaketal A, a tricyclic sesterterpenoid derived from the marine sponge *Phorbas sp.*, inhibits nitric oxide (NO) production and the expression of iNOS in LPS-stimulated macrophages. This is accompanied by reduced levels of cytokines such as TNF-α, IL-1β, and monocyte chemotactic protein-1 (MCP-1), mediated by NF-κB inhibition (Seo et al., 2015). Likewise, fucoxanthin decreased iNOS and COX2 expression, suppressed inflammatory mediators like prostaglandin E2 (PGE2) and NO, and reduced IL-1β, IL-6 and TNF-α levels, via the inhibition of NF-κB activation, strongly supporting its anti-inflammatory potential both *in vitro* and *in vivo* (K.-N. Kim et al., 2010; Yang et al., 2020).

Besides, seaweed presents many biocompounds, like proteins, polysaccharides and polyphenols, which are reported to have anti-inflammatory effects. Fucoidans exert anti-inflammatory activity, demonstrated *in vitro* and *in vivo*, through inhibition of COX-2, iNOS and NF-κB, leading to a reduction of pro-inflammatory cytokines (Sanjeewa et al., 2021). Sulfated polysaccharides, such as porphyran from red algae, have been shown to reduce oxidative stress and suppress the production of pro-inflammatory cytokines, making them valuable candidates in inflammaging (Vasconcelos and Pomin, 2018). Furthermore, bioactive compounds such as phlorotannins, fatty acid derivatives, peptides, and terpenoids found in brown algae like *Carpomitra costata* exhibit both antioxidant and anti-inflammatory effects (Susano et al., 2021). Similarly, the algal meroterpene 11-Hydroxy-1′-O-Methylamenta dione (AMT-E), a secondary metabolite isolated from the brown alga *Cystoseira usneoides*, has demonstrated anti-inflammatory effects in murine models, reducing myeloperoxidase activity, iNOS and COX-2 expression, and TNF-α, IL-1β and IL-10 levels (Zbakh et al., 2016).

Marine-derived secondary metabolites also exhibit potent effects on chronically activated immune cells. Compounds isolated from the fungal strain *Penicillium sp.* SF-5629 have been shown to reduce NO levels and PGE2 concentrations in microglial cells. These effects are mediated by the inhibition of iNOS and COX-2 expression, highlighting their potential for mitigating neuroinflammation (Ngan et al., 2017).

As mentioned, a key factor in the development of inflammaging is the progressive senescence of the immune system. In aged organisms, many other cell types also undergo senescence because the processes for clearing out senescent cells and mobilizing progenitor cells to restore cell numbers become inefficient. This breakdown in turnover may exhaust the regenerative capacity of progenitor cells, leading to the accumulation of senescent cells. In this process, as described above, cells manifest alterations in their secretome (SASP), reinforcing inflammaging and the senescence process in the surrounding environment and contributing to the aging process (Coppé et al., 2008; López-Otín et al., 2013). Hence, targeting senescence has the indirect effect of alleviating chronic inflammation (see Paragraph 3.4).

Inflammaging can also be explained by an imbalance between inflammatory and anti-inflammatory networks, which results in the characteristic low-grade chronic pro-inflammatory status. Healthy aging and longevity likely depend on a reduced tendency to trigger inflammatory responses and the effectiveness of anti-inflammatory mechanisms (Franceschi et al., 2007). Along with suppressing pro-inflamm atory cytokines, enhancing the release of the anti-inflammatory ones is crucial to restore immune balance. The polysaccharide extracted from the green algae *Coccomyxa gloeobotrydiformis* reduced pro-inflammatory cytokine levels and significantly increased the expression of IL-10, a key anti-inflammatory mediator (Dai et al., 2019). Similarly, the alkaloid 14-norpseurotin A, isolated from the South China Sea cold-seep-derived fungus *Talaromyces helicus* SCSIO41311, was shown to markedly attenuate the release of LPS-induced pro-inflammatory cytokines, including TNF-α and IFN-γ, while significantly upregulating the anti-inflammatory ones such as IL-4 and IL-10 (Qiu et al., 2024).

In light of emerging evidence, marine-derived compounds hold substantial promise in modulating age-related inflammation and immune decline, though further research is needed to understand their full potential and mechanisms of action. Future studies could explore the synergistic effects of these compounds in targeting pathways like SASP, NF-κB, and oxidative stress, opening new avenues in the development of geroprotective therapies.

3.8. Dysbiosis

The gut microbiota (GM), the collection of microorganisms

colonizing the intestinal tract (Haran and McCormick, 2021), can be considered a true organ of the body, contributing to the well-being of the host organism and influencing local and systemic processes such as nutrient conversion, maturation of mucosal immunity, gut-brain communication and vitamin supply (Weiss and Hennet, 2017). The GM of a healthy adult contains an average of 150 bacterial species, 95 % of which belong to the phyla Firmicutes and Bacteroidetes, with a Firmicutes/Bacteroidetes (F/B) ratio of 0.8/1, and the remaining 5 % to the phyla Actinobacteria, Proteobacteria, Tenericutes, Verrucomicrobia and Fusobacteria (Adak and Khan, 2019; Huttenhower et al., 2012). The gut microbiome can influence and regulate several key metabolic pathways, including the metabolism of vitamins, enzymes, bile acids and short-chain fatty acids (SCFA) such as butyrate, acetate, lactate, succinate and propionate (Francini et al., 2025; Huttenhower et al., 2012).

The GM is in a state of dynamic equilibrium with the human host and varies both within and among individuals, depending on numerous factors, including age (Haran and McCormick, 2021). The GM remodeling in the elderly includes a reduction in GM diversity and F/B ratio (decreased Firmicutes and increased Bacteroidetes), an increase in Proteobacteria, a decrease in Actinobacteria (*e.g., Bifidobacterium*), and Verrucomicrobia (*e.g.*, *Akkermansia*) (Haran and McCormick, 2021; Hopkins and Macfarlane, 2002; Mariat et al., 2009).

An alteration of metabolites regulated by the GM may also occur in aged gut. For instance, Firmicutes are widely associated with the production of SCFAs, and their age-related reduction may be associated with low butyrate production (Claesson et al., 2012) that has been linked to intestinal barrier fragility (Adak and Khan, 2019). Older people have also been found to have lower levels of acetate, lactate, succinate and propionate (Claesson et al., 2012). Conversely, the age-related increase in Proteobacteria (Gram-negative pathogenic bacteria with LPS) can promote inflammation and oxidative stress (Weiss and Hennet, 2017).

A healthy gut microbiome may have a direct impact on longevity, but, more importantly, it may influence longevity in good health (Francini et al., 2024). Conversely, a state of dysbiosis has been shown to increase senescent cell accumulation (Marcozzi et al., 2023) and to contribute to age-associated problems like cardiovascular, metabolic, liver and neurodegenerative diseases (Haran and McCormick, 2021).

A strong correlation between the abundance of Proteobacteria (mainly *Cytobacter*, *Escherichia*, *Klebsiella*, *Shigella*, *Kluyvera* and to a lesser extent *Enterobacter*) and mortality associated with existing diseases was reported (Salosensaari et al., 2021). A genetic analysis of the GM of centenarians has revealed a bacterial structure with unique characteristics, namely a greater biodiversity and abundance of health-related groups such as *Christensenellaceae* (Firmicutes) and *Akkermansia* (Mancabelli et al., 2024). Studies have reported that GM in healthy older people showed enrichment and/or increased prevalence of *Akkermansia*, *Bifidobacterium* and *Christensenellaceae* (Biagi et al., 2016) that can have a positive effect on the aging process (Kong et al., 2019). Interestingly, *Akkermansia* and *Bifidobacterium* tend to decrease in the elderly with age-related diseases (Hopkins and Macfarlane, 2002; Kim and Jazwinski, 2018; Ticinesi et al., 2017).

There is evidence that longevity and healthspan may be improved by modulating the microbiota. As an example, caloric restriction, while improving health and lifespan (Fontana et al., 2010) (see Paragraph 3.3), also has a positive effect on the GM by increasing its biodiversity and bringing it back to eubiosis (Sbierski-Kind et al., 2022). The diet is one of the major modulators of the GM. Since the microbes can use a wide range of dietary substrates, even marine compounds can be used to modify the structure of the GM in the elderly and/or increase the production of SCFAs, reducing inflammation and improving age-related gut dysbiosis.

The spirulina pigment C-PC is a good natural dietary pigment, which can be fermented by the gut microbiota and promote the growth of specific intestinal bacteria (Table 2). Supplementation of C-PC to the regular diet fed to the mice resulted in an increase in GM biodiversity, reduced levels of Bacteroidetes and bacteria associated with inflammation, and an increase in Firmicutes such as *Lachnospiraceae*, *Ruminococcaceae*, *Rikenellaceae* and *Lactobacillaceae* (Xie et al., 2019). Histological examination showed that C-PC supplementation ameliorated the morphology of the ileal and colonic tissues of the treated mice, with reduced intestinal permeability and improved barrier function, while reducing the levels of circulating LPS (Xie et al., 2019). C-PC supplementation was also proved helpful in counteracting dysbiosis induced by the chemotherapeutic cystoplatin, through the increase in Firmicutes (such as *Rombustia* and *Lactobacillus*), the reduction of pathogenic bacteria, and the increase of anti-inflammatory metabolites, together with a lower mortality in PC-treated mice (see Paragraph 4.4.) (Y. Zhang et al., 2022). In addition to C-PC, the cyanobacteria Spirulina produces extracellular metabolites with antibacterial effects, and its supplementation inhibits the growth of some pathogenic bacteria, including *E. coli* (Finamore et al., 2017). Moreover, the extracellular products of Spirulina can promote the *in vitro* growth of lactic acid bacteria (*Lactococcus sp*, *Streptococcus sp*, *Lactobacillus spp*), associated with the production of SCFA such as lactate (Claesson et al., 2012; Finamore et al., 2017), thus demonstrating the potential of this algal source for restoring eubiosis conditions.

Among microalgal carotenoids, oral administration of astaxanthin increased *Akkermansia muciniphila* in the GM of mice and increased serum levels of the SCFA acetate. Improved expression of tight junction markers between colonocytes and reduced serum LPS levels were observed in the study, again demonstrating a beneficial effect of marine compounds on the intestinal barrier and inflammation (Liu et al., 2024). Oral administration of fucoxanthin improved the richness of GM, increased the F/B ratio and increased the relative abundance of beneficial bacteria such as *Lactobacillaceae* and *Lachnospiraceae* in the GM of a mouse model of colitis (Yang et al., 2024) (Table 2; Fig. 3).

Red algae such as *Sarcodiotheca gaudichaudii* and *Chondrus crispus* added to the diet increased *Bifidobacterium longum* and reduced the incidence of *Clostridium perfringens* infection in GM of chickens with an increase of circulating SCFAs and an improved strength of the intestinal mucosa, reducing bacterial translocation into the bloodstream (Cian et al., 2015; Kulshreshtha et al., 2014).

The algal polysaccharides fucoidan, alginate and porphyran showed several beneficial effects on the GM (Table 2). *In vivo* fucoidan supplementation improved gut dysbiosis, promoting the growth of *Bacteroides*, *Faecalibacterium* – producers of SCFAs such as propionate and butyrate (Claesson et al., 2012) – and *Blautia* in obese or diabetic mice (Wu et al., 2021). The beneficial effects of fucoidan on gut dysbiosis were confirmed in humans, in an open-label randomized controlled trial reporting that fucoidan supplementation promoted the growth of Firmicutes, such as *Faecalibacterium*, *Roseburia*, *Ruminococcus*, *Clostridium*, *Blautia*, *Dorea*, *Eubacterium*, *Lachnobacterium* and *Bifidobacterium* in the GM of enrolled patients (S. Wang et al., 2023; Table S3). Most of these species are symbiotic bacteria that produce SCFA, especially butyric acid. Used as a complementary cancer therapy, fucoidan increased bacteria of the genus *Parabacteroides* in the GM of treated patients (see Paragraph 4.4) (Tsai et al., 2023). Alginate supplementation has been shown to increase *Lactobacillus*, *Bacteroides*, *Akkermansia*, *Alloprevotella*, *Weissella* and *Enterorhabdus*, while reducing harmful *Turicibacter* and *Helicobacter* levels in the gut of diabetic mice (Liu et al., 2021). An increase of *Roseburia* and *Eubacterium* was observed in obese mice fed with a porphyran supplementation (H. Wang et al., 2023).

Besides being a substrate for the GM, marine products could have important health benefits in the elderly even thanks to associated bacteria, which may enrich the bacterial enzyme array of the GM with carbohydrate-active enzyme (CAZyme). CAZyme are able to metabolize algal polysaccharides with unique structures, which are difficult to metabolize by commensal human bacteria. Porphyranase, a CAZyme present in GM of Japanese subjects, represents an interesting example. It was hypothesised the horizontal transfer of the porphyranase gene from the marine bacteria *Zobellia galactanivorans* to commensal bacteria of the

host's GM, such as *Bacteroides plebeius* (Cian et al., 2015; Hehemann et al., 2010). Porphyranase degrades porphyran to produce oligo-porphyran, a compound with greater anti-aging properties than the polymeric form (H. Wang et al., 2023), possibly contributing to the overall health of the host. Furthermore, the breakdown of marine polysaccharides by the microbiota produces beneficial SCFAs that may play a positive role in supporting physiological functions and well-being.

Taken together, these data support the beneficial effect of marine compounds in ameliorating dysbiosis by increasing GM richness, F/B ratio, and SCFA production, improving intestinal barrier function, and reducing inflammation.

4. Marine bioactive compounds for the treatment of age-related diseases

For decades, biologists and physicians have hypothesized a significant yet often overlooked connection between aging and the development of chronic human disorders (Niccoli and Partridge, 2012). Aging not only increases the susceptibility to many chronic diseases but also significantly influences their progression. Franceschi et al. proposed that chronic diseases are not merely consequences of aging and inflammaging but can also actively accelerate aging (Franceschi et al., 2018). In this way, chronic diseases can be viewed as manifestations of accelerated aging, establishing a bidirectional relationship between aging and chronic diseases progression. Aging, age-related diseases (ARDs), and geriatric syndromes are interconnected through sharing common biological processes, forming a continuum from healthy aging to disease. While centenarians represent a model of decelerated aging, the early onset of severe ARDs in middle age is indicative of accelerated aging. Whether an individual follows a trajectory of accelerated or decelerated aging depends on their genetic background interacting lifelong with environmental and lifestyle factors (Franceschi et al., 2018). Conditions such as AD, Parkinson's disease (PD), cardiovascular diseases (CVD), diabetes, cancer, osteoarticular problems, and chronic obstructive pulmonary disease (COPD) exemplify this link, highlighting the critical need to understand aging as a central driver of these pathologies.

4.1. Neurodegenerative diseases

AD is one of the most prevalent ARDs. It is a slowly progressive and irreversible neurodegenerative disorder characterized by the accumulation of amyloid-β (Aβ) plaques, hyperphosphorylated Tau tangles and widespread neuronal loss, above all in the medial temporal lobe and neocortical structures (De-Paula et al., 2012). With someone developing dementia every three seconds, the global burden is staggering, with 55 million people affected in 2019, a number expected to rise to 139 million by 2050, as projected by the WHO (World Health Organization, 2021a). Addressing this growing crisis requires innovative therapeutic approaches, and marine-derived compounds have emerged as a promising frontier. Many of them have been tested *in vitro* and *in vivo*, and some have reached the clinical phases (Hu et al., 2023). Their potential benefits, supported by increasing research, highlight their role in mitigating the devastating impact of AD.

Marine compounds targeting AD can be grouped into three main categories based on their mechanisms of action: those that inhibit Aβ aggregation, those that block β-secretase activity, and those that suppress acetylcholinesterase activity. These distinct therapeutic strategies highlight the multifaceted potential of marine-derived molecules in addressing the pathological hallmarks of AD and improving cognitive outcomes.

Marine-derived compounds have demonstrated significant potential in targeting Aβ aggregation. For example, lodopyridone A, an alkaloid isolated from the marine-derived actinomycete of the genus *Saccharomonospora*, reduced Aβ production by up to 49 % in SH-SY5Y neuroblastoma cells (Le et al., 2017). Similarly, compounds extracted from the green alga *Caulerpa racemosa* have shown neuroprotective effects against $A\beta_{25-35}$-induced toxicity in SH-SY5Y cells. Specifically, α-tocospirone improved cell viability by 13.6 % (Yang et al., 2015), while racemosin A and B, unique bisindole alkaloids, significantly alleviated $A\beta_{25-35}$-induced damage (Liu et al., 2013). Bryostatin 1, derived from the marine invertebrate *Bugula neritina*, prevented Aβ increase and AD symptoms in mouse models of AD, and was tested in clinical trials with AD patients, where it demonstrated safety, tolerability, and positive preliminary data on efficacy, although needing further validation (Hu et al., 2023; NCT02221947; Table S3).

In addition to inhibiting Aβ aggregation, certain marine compounds also target the amyloidogenic pathway by blocking β-secretase (BACE-1) activity. Fucofuroeckol-b, an eckol derivative from the brown alga *Eisenia bicyclis* (Lee and Byun, 2018), and saccharochlorines A and B, isolated from the saline culture of *Saccharomonospora* (Le et al., 2020), both exhibited potent BACE-1 inhibition in SH-SY5Y cells.

The inhibition of acetylcholinesterase (AChE) activity, a key therapeutic target in AD, has also been promoted by several marine-derived compounds. For instance, marinoquinoline A, a pyrroloquinoline alkaloid isolated from a novel marine gliding bacterium species, *Rapidithrix thailandica*, has demonstrated potent AChE inhibitory activity. This mechanism is particularly relevant in AD therapy, as the inhibition of AChE enhances cholinergic signaling by preventing the breakdown of acetylcholine, thus partially mitigating cognitive decline associated with the disease. Such findings highlight the diverse therapeutic applications of marine-derived molecules in addressing multifactorial aspects of AD pathology (Sangnoi et al., 2008).

Finally, astaxanthin was shown to reduce the age-related neuroinflammation in aging female rats and to delay the age-related cognitive decline in a mouse model of accelerated aging, offering a further cue for the treatment of neurodegenerative diseases, also because it seems able to penetrate the BBB (Balietti et al., 2016; Fu et al., 2023). A recent clinical trial, still unpublished investigated the possible effect of astaxanthin on Alzheimer's patients from 60 to 90 years old (NCT05015374; Table S3).

PD is a rapidly progressing neurodegenerative disease with recognizable clinical symptoms and the second most common neurodegenerative disease, affecting 2–3 % of individuals aged 65 and older (Poewe et al., 2017). The neuropathological hallmarks of PD include striatal dopamine deficiency, driven by the loss of dopaminergic neurons in the *substantia nigra*, and the presence of Lewy bodies, intracellular inclusions primarily composed of aggregated α-synuclein (Poewe et al., 2017). Recently, inflammaging was proposed as one of the key processes underlying PD (Calabrese et al., 2018). As discussed in paragraph 3.7, inflammaging reflects an exaggerated activation of aging-related pathways, and PD could be viewed as a pathological amplification of these processes.

Marine-derived natural compounds have shown promise for PD treatment by targeting key pathological mechanisms. Notably, these compounds demonstrate the potential to combat α-synuclein aggregation, as well as inhibit monoamine oxidase-B (MAO-B), an enzyme that metabolizes dopamine. Elevated MAO-B activity produces ROS, exacerbating oxidative stress and directly damaging dopaminergic neurons (Nagatsu and Sawada, 2006). This dual-target approach positions marine-derived compounds as valuable candidates for developing novel pharmacological strategies to mitigate PD progression.

Marine-derived compounds exhibit potential as neuroprotective agents in PD models. NP7, a compound derived from *Streptomyces* sp., is a potent antioxidant, that prevents apoptosis and necrosis induced by H_2O_2 in neurons and glial cells *in vitro* and in a murine model of PD. Additionally, it inhibits microglial activation and suppresses H_2O_2-induced phosphorylation of ERK, marking it as a promising candidate for protecting dopaminergic neurons from oxidative stress (Mena et al., 2009). Interestingly, NP7 is believed to cross the blood-brain barrier (BBB) (Mena et al., 2009), which makes the brain not permeable to many compounds and hamper the use of drugs to treat neurodegenerative disorders. Brain-penetrating molecules, *e.g.* substrates of the

membrane transporters present in the BBB, can be used to overcome this challenge: indeed, the so-called pro-drug approach uses such molecules chemically coupled with drugs to favour the entry of drugs in the brain, as trojan horses (Patel et al., 2009). In this scenario, marine compounds may represent a large basin of novel potential BBB-penetrating substrates to be conjugated with drugs.

Fucoidan demonstrated strong neuroprotective effects in a PD mouse model, mitigating behavioural deficits. These effects were likely mediated by elevating dopamine and its metabolites and increasing tyrosine hydroxylase expression (Luo et al., 2009). Similarly, in a rat PD model, sulfated agaran, a polysaccharide from *Gracilaria cornea*, reduced oxidative and nitrosative stress, improved motor deficits, and modulated neurotransmitter levels by increasing dopamine and decreasing serotonin (Souza et al., 2017). Additionally, sulfated agaran increased levels of GSH and the BDNF gene transcription. Overall, sulfated agaran may protect against brain damage, suggesting it could help treat neurodegenerative diseases (Souza et al., 2017).

Spirulina platensis has emerged as a promising source of neuroprotective compounds. Its protein extract and phycocyanin exhibit potent antioxidant activity, primarily by enhancing the activity of cellular antioxidant enzymes. These properties have demonstrated neuroprotective effects in an α-synuclein-induced neurotoxicity model of PD (Pabon et al., 2012). Furthermore, *Spirulina* polysaccharides have been shown to protect against neurotoxin-induced dopamine loss in mice, emphasizing their role in preserving dopaminergic neurons and mitigating PD-related neurodegeneration (Zhang et al., 2015).

4.2. Cardiovascular diseases

Cardiovascular diseases (CVDs) are among the most prevalent ARDs, as well as the main cause of death in the aging population (>70) (World Health Organization, 2021b). During aging, the cardiovascular functionality progressively declines, due to cellular and physiological alterations, such as cardiomyocyte senescence and hypertrophy, reduced cardiomyogenesis, cardiac fibrosis, systemic inflammation, endothelial senescence and dysfunction (Hastings et al., 2024). The aging of the cardiovascular system increases the risk of developing CVDs, mainly heart failure, atherosclerosis, thrombosis, stroke, myocardial infarction, and coronary artery disease (Qu et al., 2024).

Notably, to date one marine product has been marketed for CVDs prevention, the fish-derived omega-3-acid ethyl esters, approved for the treatment of hypertriglyceridemia (Ferrari et al., 2020). Moreover, some marine compounds are/have been under evaluation in several clinical trials for CVDs, including fish-derived omega-3 polyunsaturated fatty acids, as well as the polysaccharide alginate, the microalgae *Spirulina maxima* and astaxanthin (Table S3). While the effectiveness of polyunsaturated fatty acids in cardiovascular protection is still debated (Sherratt et al., 2023), alginate hydrogels are promising scaffolds for cardiac regeneration after heart injury (see Paragraph 3.5) (Cattelan et al., 2020), and *S. maxima* achieved good results as an anti-hypertensive in a pilot clinical study (Martínez-Sámano et al., 2018). So far, the effect of astaxanthin on arrhythmias and stroke is still under clinical investigation (NCT02087033, NCT01647984, and NCT03945526).

Since many marine compounds display anti-inflammatory and antioxidant mechanisms of action, the interest in developing marine-derived drugs for CVDs treatment is increasing (Akram et al., 2023; Giuliani et al., 2024). Indeed, many marine anti-inflammatories and antioxidants demonstrated the capacity to reduce or prevent atherosclerotic plaques *in vivo*, above all the polysaccharides fucoidan and the carotenoid astaxanthin, whose anti-atherogenic effect was well established in different animal models (Giuliani et al., 2024). The anti-inflammatory action of micoepoxydien and asperlin, secondary metabolites of fungal origin, counteracts the formation of macrophage foam cells and consequent plaque formation (Xia et al., 2015; Zhou et al., 2017), and xyloketal B, a potent polyphenolic antioxidant also of fungal origin, has been shown to reduce atherosclerosis and endothelial dysfunction (Zhao et al., 2015). More recently, another potent free radical scavenger, echinochrome A, a pigment found in sea urchin needles, gained attention for CVDs treatment. Echinochrome A displayed cardioprotective functions in animal models by attenuating cerebral ischemic injury and myocardial ischemia/reperfusion injury and preventing chronic heart failure (X. Tang et al., 2023).

Furthermore, several marine compounds prevent atherogenesis through a lipid-lowering activity, including, again, astaxanthin (Kumar et al., 2017; Ryu et al., 2012) and fucoidan (Park et al., 2016; Yokota et al., 2016), but also sea cucumber saponins (Han et al., 2019), the sponge-derived manzamine A (Eguchi et al., 2013), and the algal product saringosterol (Yan et al., 2021). Specific mechanisms of action include: for fucoidan, activation of PPARα pathway, with consequent regulation of fatty acid β-oxidation; for saponins, regulation of gut microbiota diversity and genes related to lipid synthesis; for manzamine A, inhibition of acyl-coenzyme A:cholesterol acyl-transferase (ACAT) activity, which plays a central role in intestinal absorption of cholesterol; for saringosterol, activation of Liver X receptor β, with consequent regulation of genes involved in cholesterol metabolism.

Among marine products with *in vivo* evidence of anti-coagulative, anti-platelet and anti-thrombotic activities, it is worth mentioning fucoidan, sulphated glycans of algal or sea urchin origin, the sponge-derived alkaloid fascaplysin, the sea cucumber triterpenoid frondoside A, the crab peptide tachyplesin I, and R-/S-2-(2-Hydroxypropanamido) benzoic acid (R-/S-HPABA), a small organic molecule isolated from a marine fungus (Dwivedi and Pomin, 2020).

Finally, several peptides from different marine sources (brown and red algae, sea cucumbers, and fish species) demonstrated anti-hypertensive action through angiotensin-I-converting enzyme (ACE) inhibition (Deng et al., 2018; Ko et al., 2012; Wijesekara and Kim, 2010). This opens interesting implications for cardiovascular therapies and prevention, since hypertension is one of the main risk factors for CVDs, and ACE inhibitors are among the most common and effective drugs for the control of blood pressure.

4.3. Diabetes

Type 2 diabetes mellitus (T2DM) is another widespread disease of aging, characterized by a chronic course and by an increasing incidence in older adults, with around 20 % aged people (>65) affected worldwide (Sinclair et al., 2020). The main trait of T2DM is hyperglycaemia, resulting from an altered glucose homeostasis and metabolism. Pancreatic islets, indeed, as other organs, experience the accumulation of senescent cells, affecting insulin secretion (Narasimhan et al., 2021). Insulin resistance, involving the regulation of glucose transport in liver, skeletal muscle and adipocyte cells, also increases with aging and plays a critical role in the pathogenesis of T2DM. Frequently, T2DM is associated with complications, such as atherosclerosis, nephropathy, neuropathy, retinopathy, frailty and disability. Although several drugs are available for the treatment of T2DM, the chronic use and the presence of side effects and comorbidities requires a continuous search for novel therapies.

Various marine products have been investigated for their hypoglycaemic activities, although none of them achieved a conclusive level of efficacy (Giuliani et al., 2024). Marine compounds may exert an anti-diabetic effect via two main different mechanisms: i) the inhibition of α-glucosidase and α-amylase activity, to reduce the intestinal absorption of glucose (like the widely prescribed anti-diabetic acarbose), and ii) the activation of the AMPK/Akt pathway (like metformin), to regulate the hepatic metabolism of glycogen and stimulate the uptake of glucose by skeletal muscle through upregulation of glucose transporters (*e.g.* GLUT4) (Giuliani et al., 2024). The main findings are summarized below.

The anti-diabetic properties of fucoxanthin are supported by several evidence in murine models: this carotenoid alleviates hyperglycaemia

and insulin resistance through activation of Akt signaling in liver and skeletal muscle, with upregulation of insulin receptor and GLUT4 transporter, and improvement of glucose metabolism and glycogen synthesis (Y. Zhang et al., 2018). The efficacy of fucoxanthin in enhancing insulin secretion was confirmed in a recent clinical study on patients affected by metabolic syndrome, together with a tendency to improve insulin sensitivity; however, no effects were observed on glucose levels, probably due to the normoglycemic condition of enrolled subjects (López-Ramos et al., 2023; Table S3). Future studies on pre-diabetic or diabetic patients could better confirm fucoxanthin effects observed in preclinical models.

Dieckol, a polyphenolic compound extracted from the brown algae *Ecklonia cava*, displayed anti-diabetic properties in mice and zebrafish models, mediated both by α-glucosidase and α-amylase inhibitory activity (higher than acarbose) and by activation of the Akt pathway, as well as the regulation of glucose transport and hepatic glucose metabolism (E.-A. Kim et al., 2016; Lee et al., 2010). Dieckol-rich extracts from the algae *Ecklonia cava* were tested in two double-blind, randomized clinical trials in eighty and twenty, respectively, pre-diabetic patients, both demonstrating a lowering effect on postprandial blood glucose, with no associated side effects but discordant results on improvement of insulin resistance (Almutairi et al., 2023; Lee and Jeon, 2015; Table S3).

Fucoidan has displayed promising anti-diabetic properties in preclinical models (through α-glucosidase and α-amylase inhibition, AMPK activation, gut microbiota modulation), but some performed clinical studies have not yet demonstrated a clear effect in humans (Giuliani et al., 2024; Liu et al., 2025; Table S3).

A 2010 clinical study enrolling one hundred T2DM patients proposed marine collagen peptides from fish hydrolysates for the treatment of diabetes, since they significantly lowered the levels of fasting blood glucose and insulin and of human glycated haemoglobin, while improving insulin sensitivity and plasmatic lipid levels (Zhu et al., 2010; Table S3). Mechanistic insights were obtained more recently in a rat model of diabetes, where the hypoglycaemic effect of fish collagen peptides was explained by the regulation of the hepatic metabolism of glycogen, to an extent comparable to that of metformin (Lin et al., 2023).

Notably, beneficial effects on blood glucose levels and insulin resistance were suggested for the microalgae *Chlorella vulgaris* in patients with non-alcoholic fatty liver disease (Ebrahimi-Mameghani et al., 2017).

Many other marine products, especially from brown and green algae, have been proposed for the treatment of diabetes upon observation of hypoglycaemic properties in *in vivo* models. Among the most interesting are two algal-derived phlorotannins: diphlorethohydroxycarmalol acts as a strong α-glucosidase and α-amylase inhibitor and promotes glucose uptake into skeletal muscle, demonstrating hypoglycaemic effects in mice and zebrafish models (Heo et al., 2009; Yang et al., 2021); octaphlorethol A was shown to alleviate hyperglycaemia, stimulate GLUT4-mediated glucose uptake by skeletal muscle and reduce hepatic gluconeogenesis in mice (Lee et al., 2016a, 2016b).

4.4. Cancer

Although it can affect even children and young people, cancer is considered a disease of aging, since its incidence steeply increases in advanced age ("The importance of aging in cancer research," 2022), and it remains the second leading cause of death worldwide in people over 70, after cardiovascular diseases (Woo 2021). Among the different cancer types, lung, colorectal, prostate, breast and stomach cancers are the most represented in individuals > 65 (Pilleron et al., 2019). Cancer and aging share some biological traits, namely genomic instability, inflammation, and metabolic changes. With advancing age, DNA damage and mutations accumulate, increasing the risk of tumour development (Montégut et al., 2024). Meanwhile, the accumulation of senescent cells (and consequent production of SASP molecules) may induce a chronic inflammation that generates a tumour-permissive microenvironment (Marcozzi et al., 2023), making older people more susceptible to tumour occurrence. Moreover, cancer is characterized by dramatic metabolic changes that negatively affect aged patients, who may experience more adverse effects from drugs (Berben et al., 2021), since they are often characterized by suboptimal clinical status (*e.g.* frailty, comorbidities), and anti-cancer therapies can significantly reduce quality of life. Thus, despite the wide amount of existing anti-cancer drugs, the request for innovative drugs is still ongoing, and the research of anti-cancer from marine sources is experiencing an exponential growth (Dyshlovoy and Honecker, 2022; Nigam et al., 2019).

The importance of marine sources for the management of cancer is undoubted: i) the first marine-derived approved molecule, cytarabine, is an anti-cancer drug, still in use for the treatment of leukemia, ii) twelve anti-cancer drugs have a marine origin (*i.e.* Cytarabine, Fludarabine, Nelarabine, Brentuximab vedotin, Trabectedin, Eribulin, Lurbinectedin, Polatuzumab vedotin, Enfortumab vedotin, Belantamab mafodotin, Tisotumab vedotin-tftv, Disitamab vedotin), out of a total of seventeen marine-derived drugs approved for clinical use (Dyshlovoy and Honecker, 2022), iii) several marine compounds has undergone clinical trials for cancer therapy (Cappello and Nieri, 2021) and iv) those under pre-clinical research for anti-cancer potential are many and exponentially growing. Exemplifying lists of the many marine-derived molecules with tumour suppression mechanisms of action (including anti-tubulin, apoptotic, autophagy induction, kinase inhibitors, angiogenesis inhibitors, inhibitor of hypoxia-inducible factor, topoisomerase inhibitors, Wnt signaling inhibitors) have been presented elsewhere (Dalisay et al., 2024; Nigam et al., 2019; Saeed et al., 2021).

Interestingly, for some of the marine FDA-approved anti-cancer drugs the transporters responsible for their distribution have been identified: i) cytarabine is recognized by several ABC transporters (ABCC4 (Drenberg et al., 2016), ABCC10 and ABCC11 (Di Francia et al., 2021)) and SLC transporters (OCTN1 (Drenberg et al., 2017), ENT1, ENT2 and CNT3 (Di Francia et al., 2021)); ii) fludarabine and nelarabine are recognized by ENT-type transporters (Colomer et al., 2003; Yamauchi et al., 2014); iii) trabectedin is recognized by several ABC transporters (ABCB1, ABCC2, ABCC3 (Beumer et al., 2007; Van Waterschoot et al., 2009)); iv) blenrap is substrate of the ABC transporters MRP1,2,3 and of the SLC transporters OATPB1 (Baines et al., 2022) and 3; v) lurbinectedin is substrate of MDR1 and inhibitor of OATB1P1, 3, OCT1 and MATE1 (Singh et al., 2021).

Among marine compounds with anti-cancer properties, several are of particular interest for those cancers typical of advanced age. Many marine molecules were tested *in vitro* for their activity against prostate cancer cell lines (Montuori et al., 2023), numerous *in vitro* and *in vivo* studies were done on marine candidates for the treatment of colorectal cancer (Han et al., 2022), and also, breast cancer may be targeted by marine compounds (De Sanctis et al., 2022).

Some marine molecules also represent intriguing candidates as a complementary cancer therapy, to alleviate the side effects of chemotherapeutic drugs. In a clinical trial with patients affected by locally advanced rectal cancer (NCT04342949), low-molecular weight fucoidan was found to ameliorate the quality of life and several chemotherapy adverse events (Tsai et al., 2023). Interestingly, around 50 % of patients receiving fucoidan therapy were over 65 years old. A similar protective effect against chemotherapy-induced damage was also observed for C-PC, which alleviates oxidative damage and inflammation in mice treated with the anti-cancer cisplatin, reducing their mortality (Y. Zhang et al., 2022). For both fucoidan and C-PC, the effects were mediated by a modulation of gut microbiota (see Paragraph 3.8) (Tsai et al., 2023; Y. Zhang et al., 2022).

4.5. Musculoskeletal disorders

Bone and joint health is fundamental for maintaining mobility,

independence and overall well-being. As people age, there is a noticeable decline in bone mass, quality and function, potentially leading to osteoporosis – a systemic skeletal disorder and a major cause of fractures worldwide (Corrado et al., 2020). Several factors contribute to bone loss, including increased osteoclast activity (Chung et al., 2014), a decrease in the pool of osteoprogenitors with age (Bergman et al., 1996) and reduced osteoblasts differentiation capacity (Becerikli et al., 2017). The weakening of bone architecture in osteoporosis not only increases fracture risk but also exacerbates joint degeneration, creating a complex interplay between bone fragility and joint dysfunction (Huang and Cai, 2024). Simultaneously, osteoarticular disorders – including osteoarthritis, rheumatoid arthritis and other inflammatory or degenerative diseases - contribute to pain and loss of function, since they are characterised by changes in cartilage, synovial fluid and periarticular structures (Grässel et al., 2021; Peng et al., 2025). Aging is also often associated with sarcopenia, a chronic condition that involves a progressive decline in skeletal muscle mass, strength and functionality. Sarcopenia has a great impact on the life of older people, since it is associated with mobility limitations, physical frailty, increased risk of falls, loss of autonomy, and higher mortality rates (Cruz-Jentoft and Sayer, 2019).

Given the increasing demand for novel therapeutic options to support and manage the symptoms of musculoskeletal diseases, marine molecules have emerged as promising candidates due to their diverse chemical structures and potential pharmacological properties.

Hymenialdisine (HMD) is a marine sponge–derived natural inhibitor of protein kinases with promising applications for osteoarthritis and osteoporosis treatment. Anti-osteoarthritis properties of HMD were first established in bovine cartilage disks and in cultured chondrocytes, where HMD was able to inhibit proteoglycan degradation and promote its synthesis (Badger et al., 1999). More recently, HMD was shown to suppress osteoclastogenesis and promote osteoblast differentiation and mineralization *in vitro*, and to reverse bone loss in a mouse model of osteoporosis (Wang et al., 2020).

Astaxanthin is another interesting candidate for bone problems (Davan et al., 2023). *In vitro* studies in mouse-derived neural stem cells treated with astaxanthin showed an increased osteogenic and adipogenic differentiation (Kim et al., 2010b), as well as in human bone-derived mesenchymal stromal cells, in which osteogenic differentiation was in a dose-dependent manner (G. Zhao et al., 2020). In *in vivo* rat models of osteoarthritis, astaxanthin mitigated articular cartilage degradation and osteoarthritis progression by inhibiting chondrocyte ferroptosis and regulating mitochondrial function (Wang et al., 2022a) and reduced joint cartilage damage through attenuating activated macrophage-related inflammation (Zhu et al., 2023).

Astaxanthin efficacy as treatment against osteoarthritis was also confirmed in a mouse model, where attenuation of subchondral bone destruction, articular cartilage damage and inflammation were observed, mediated by Sirt1 upregulation (Qin et al., 2024). Recently, given the promising effect of astaxanthin, a new formulation was developed, namely a folic acid-modified liposomal nanoparticle loaded with astaxanthin (AST@Lip-FA), which improved solubility, stability and the delivery to the joint site, with a significant increase of the therapeutic efficacy *in vitro* and a mouse model of osteoarthritis (Zhao et al., 2024).

Marine omega-3 polyunsaturated fatty acids were explored for the management of sarcopenia in various randomized clinical trials involving older subjects. Although the results are not yet well established, the supplementation of omega-3 is generally beneficial for muscle mass and strength, with mechanisms including improved mitochondrial function, lower inflammation and proteolysis, and modulation of neuromuscular junction activity (Therdyothin et al., 2023; Table S3). Besides omega-3 fatty acids, in recent years, other marine products have gained particular attention for their anti-sarcopenic properties. The effect of Fermented Sarco Oyster (FSO) extract, derived from the bivalve *Crassostrea gigas*, was investigated in a clinical trial including 52 postmenopausal women. FSO supplementation increased quadriceps muscle extension, handgrip strength, and plasmatic levels of IGF-1 (Rheu et al., 2022; Table S3). Such effect has been ascribed to the high content of the GABA neurotransmitter, which is enriched in FSO after fermentation, and three underlying mechanisms were suggested, namely increased autophagy, decreased muscle inflammation, and increased satellite cell function (Byun et al., 2023).

In vivo evidence in murine models of muscle atrophy suggests that the loss of muscle mass may be prevented by dietary supplementation of astaxanthin and fucoxanthin, with effects observed for the soleus muscle and the tibialis anterior muscle, respectively. Astaxanthin stimulates mitochondrial biogenesis and inhibits mitochondrial ROS production and mitochondrial-mediated apoptosis, while reduction of muscle lipid peroxidation was observed after fucoxanthin treatment (Sun et al., 2021; Yoshikawa et al., 2021).

The brown algae *Ishige okamurae* (IO) and its active compound, the phlorotannin DPHC, displayed anti-sarcopenic effects in an *in vivo* aging mouse model. Old mice supplemented with IO and DPHC displayed improved lean mass and muscle function, measured as grip strength and time required for ladder climbing, with increased weight and thickness of gastrocnemius and soleus, and improved histological parameters of myofibers (Hyun et al., 2022). Regarding the mechanisms, decreased inflammatory proteins and muscular proteolytic pathways (atrogin-1, muscle RING-finger protein-1 (MuRF-1), and FoxO3) were observed, as previously demonstrated *in vitro* in myotubes, with involvement of the NF-κB pathway and/or Akt activation (Hyun et al., 2022; Kim et al., 2020).

Other marine products, *i.e.* the protein extract of the red algae *Pyropia yezoensis* (PYCP), protein hydrolysate from *Spirulina platensis*, and hydrolysates of *Crassostrea nippona* (bivalve), were shown to alleviate myotube atrophy and promote myotube formation *in vitro*. Their targets were key proteins involved in the progression of sarcopenia, *i.e.* components of the ubiquitin-proteasome system (atrogin-1, MuRF-1, Foxo-3a) or myogenic proteins (myogenin, MyoD, myosin), through activation of the Akt pathway and inhibition of the proinflammatory NF-κB pathway (Kurera et al., 2024; Lee et al., 2022; Lee et al., 2021).

4.6. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a lung disorder primarily characterized by progressive airflow limitation and tissue destruction due to chronic inflammation (Singh et al., 2019). As the fourth leading cause of death globally, COPD accounted for approximately 3.5 million deaths in 2021, representing about 5 % of all global mortality (World Health Organization, 2024). Notably, the prevalence of COPD significantly increases with age, highlighting its status as a typical aging-related disease. Age-associated changes in lung structure and function may predispose elderly individuals to COPD by exacerbating their susceptibility to the disease's pathogenesis. Indeed, evidence shows that the prevalence of COPD in the U.S. population rises from around 6.6 % in individuals aged 45–54 to approximately 12 % in those over 64 years old (Centers for Disease Control and Prevention CDC, 2012).

Most marine bioactive compounds have been explored in the context of other ARDs, leaving the field of COPD research relatively neglected. Despite this, emerging evidence highlights the potential of marine-derived compounds in addressing COPD-related inflammation and oxidative stress.

One notable compound is fucoxanthin, which has demonstrated an ability to inhibit TGF-β1-induced phosphorylation of key signaling molecules, including p38 MAPK, PI3K/Akt, and Smad2/Smad3, in a bleomycin-induced lung fibrosis model (Ma et al., 2017). Moreover, it has shown efficacy in reducing oxidative damage and inflammation in cigarette smoke extract (CSE)-induced bronchial epithelial cells from COPD patients by regulating the PPARγ/NF-κB pathway (Chen et al., 2022).

Another promising compound is brevenal, a polyether produced by the dinoflagellate *Karenia brevis*, that decreases the pro-inflammatory chemokine IL-8 and reduces TNF-α production induced by LPS in human lung epithelial cells and macrophages, respectively. Additionally, brevenal has been shown to restore the toxin-induced dysfunction of mucociliary clearance at picomolar concentrations in an animal model of asthma (Abraham et al., 2005; Keeler et al., 2019). Finally, astaxanthin has demonstrated protective effects in the airway epithelium, where it attenuates cigarette smoke extract-induced apoptosis by reducing oxidative DNA damage (H. Tang et al., 2023).

5. Conclusions

Marine products are attracting increasing interest for their gerontological potential. The marine environment, a largely untapped resource, holds considerable potential for advancements in gerosciences. Its exploration could improve aging, healthspan, longevity, and the management of age-related conditions. This review highlighted the broad spectrum of promising compounds for the management of aging. As reported in Chapter 2 and 3, at least twenty compounds were identified for their ability to prolong the lifespan (Table 1), and 23 were described to target at least two of the so-called hallmarks of aging (Fig. 1; Table 2). Among the hallmarks targeted by marine molecules, macroautophagy seems to be the most identified or studied; deregulated nutrient sensing is also among the most described targets for marine products (Fig. 2). The importance of nutrient sensing in the aging process, demonstrated by the benefits of caloric restriction as a prolongevity strategy, highlights the sea as a remarkable opportunity to seek geroprotective compounds. Conversely, very little is known about the potential of marine molecules in modulating epigenetic modifications and telomere attrition to counteract the aging decline (Fig. 2). Since these are classified as primary hallmarks of aging (*i.e.* the primary causes of aging), the activity of marine products on them represents an interesting aspect to be further investigated. The ability of some marine products to activate the histone deacetylases Sirtuins *(i.e.* crude extracts of *M. fluostatini* and *B. licheniformis*, xyloallenoide A derivative C3, *M. edulis* peptides, and fucoxanthin) may suggest an effect on histone modifications, but studies confirming these modifications, the maintenance of heterochromatin stability and consequences on downstream gene expression are lacking. Importantly, no investigations have explored the activity of marine molecules on DNA methylation patterns, which undergo profound age-associated changes, being also able to discriminate among different rates of aging decline, so that they have been proposed as predictors of biological age (the so-called “epigenetic clocks”). Also, the inhibition of retrotransposable elements, whose epigenetic and transcriptional derepression has been proposed as a hallmark of aging and a trigger of inflammaging (De Cecco et al., 2019), has not been covered by studies on marine compounds, and many marine molecules with anti-viral properties could offer an interesting basin to explore retro-transcriptase inhibitory properties. Similarly, the discovery of marine telomerase activators, which could attenuate telomere attrition, is still missing, since the major research effort has to date been concentrated on compounds with telomerase inhibitory activity, due to their anticancer potential.

Molecules with the most widely demonstrated and/or studied anti-aging effects – including life extension activities, capacity to target multiple hallmarks, as well as pharmacological properties against age-related diseases – were fucoxanthin, astaxanthin, and fucoidan (Fig. 1). Among them, fucoxanthin was proven to target the highest number of hallmarks of aging (9 out of 12), from genomic instability to dysbiosis, regulating key pathways, *e.g.* Sirt1, AMPK, Nrf2, UCP, connexins and NF-κB (Fig. 3). Its potential in the management of aging condition is further enforced by its properties towards the treatment of age-related pathologies like diabetes, sarcopenia, and COPD. Astaxanthin is the marine molecule with the most translatable prolongevity potential, with strong evidence of lifespan extension in outbred mice in an ITP program (Harrison et al., 2024). Implicated in contrasting several important aging processes (*e.g.*, DNA damage, autophagy and mitochondrial impairment, loss of stemness, inflammation, dysbiosis) (Fig. 3), its possible effect on senescent cells is still unexplored and worthy of future investigations, given the central role of senescence in determining the occurrence of aging signs. Astaxanthin also has interesting properties to treat various age-related disturbances, like neuroinflammation and cognitive decline, stroke, atherosclerosis and other cardiovascular problems, osteoarthritis, sarcopenia, and COPD. Fucoidan modulates key aging targets (*e.g.*, sirtuins, DNA integrity, senescence, staminal pool, inflammatory pathways, and GM) (Fig. 3) and holds several properties to counteract aging decline, *i.e.* neuroprotective, anti-atherogenic, anti-thrombotic, anti-diabetic, as well as being able to mitigate the adverse effects of chemotherapy. Among the molecules that increase lifespan, porphyran demonstrated a good potential in counteracting aging processes like senescence, inflammation and dysbiosis. This algal polysaccharide, as well as its derivatives, gained particular attention also for its hypolipidemic, hypoglycaemic, and neuroprotective properties, encouraging further research on its potential to treat age-associated conditions (Wang et al., 2023). Marine peptides also attracted increasing interest for their prolongevity properties and may deserve further investigation on their mode of action. The life extension induced by *M. edulis* peptides could be linked to the modulation of Sirt1, mitochondrial function and senescence, which was observed for oligopeptides (< 1 kDa) derived from the same mollusc (Zhou et al., 2014). Similarly, *A. leucoprocta* peptides, showing lifespan extension properties, could act through regulation of AMPK and mitochondrial function, as observed for SCP-1 and −2 peptides, obtained from the same sea cucumber (Wang et al., 2021).

Despite the absence of a proven effect on lifespan, some marine molecules can target multiple hallmarks, making them interesting candidates for longevity studies (Fig. 1). Among them, 3-BDB may have a protective role towards a wide range of key aging mechanisms, from DNA and mitochondrial damage to cellular senescence and inflammation. However, its mechanism of action needs further elucidations. Similarly, PA-S14 is involved in crucial processes, *i.e.* macroautophagy, mitochondrial function, nutrient sensing and senescence, with a known cellular target identified as the LK-B1. Interestingly, C-PC, together with a beneficial modulation of autophagy, cellular senescence and dysbiosis, may have a role in the protection of the staminal pool, in particular the mesenchymal compartment that could be severely compromised during aging, predisposing to osteoarticular disorders. Further studies on these molecules could better elucidate their mechanisms of action, their effect on other crucial hallmarks of aging and a possible *in vivo* role on healthspan and longevity.

Despite numerous marine products demonstrated to have a prolongevity effect in yeast, fly and worm models, very few molecules were shown to extend the lifespan of mammalian models, *i.e.* only astaxanthin and marine collagen peptides from the salmon *O. keta*, tested on mice and rats, respectively. An intensification of studies on mammalian models and a more profound knowledge of the mechanism of action of marine compounds with prolongevity and geroprotective properties would be essential for their potential applicability in the gerosciences. Moreover, our research highlights a limited translation of preclinical findings to clinical practice. Indeed, only a few of the described compounds have already entered clinical trials (Table S3), while the majority of them is still investigated at the preclinical stage. More importantly, there is an almost absolute lack of trials carried out in the aged human population for testing the effects of marine compounds on aging outcomes. Rare examples are represented by fucoidan, which exerts a beneficial modulation of microbiota in patients > 65 years old under chemotherapy (Y. Zhang et al., 2022), and two marine products tested in the context of sarcopenia, *i.e.* omega-3 fatty acids (Therdyothin et al., 2023) and FSO (Rheu et al., 2022).

Overall, the vast diversity of marine bioresources suggests untapped potential, warranting further research to unravel their mechanisms and

translate these findings into effective interventions for age-related conditions. An integrated and multidisciplinary approach, including expertise and knowledge from geroscience, marine biology and pharmacology, will ensure a step forward in the application of marine compounds as anti-aging. As suggested by the One Health approach (World Health Organization, 2023), a close collaboration among different disciplines will promote the valorization of the ocean as a resource to face the major global sanitary challenges, highlighting a close interaction between human and ocean health. In this sense, marine geroprotectors may represent the next wave of anti-aging medicine.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Given her role as Editorial Board Member, D.M. had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2025.102935.

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