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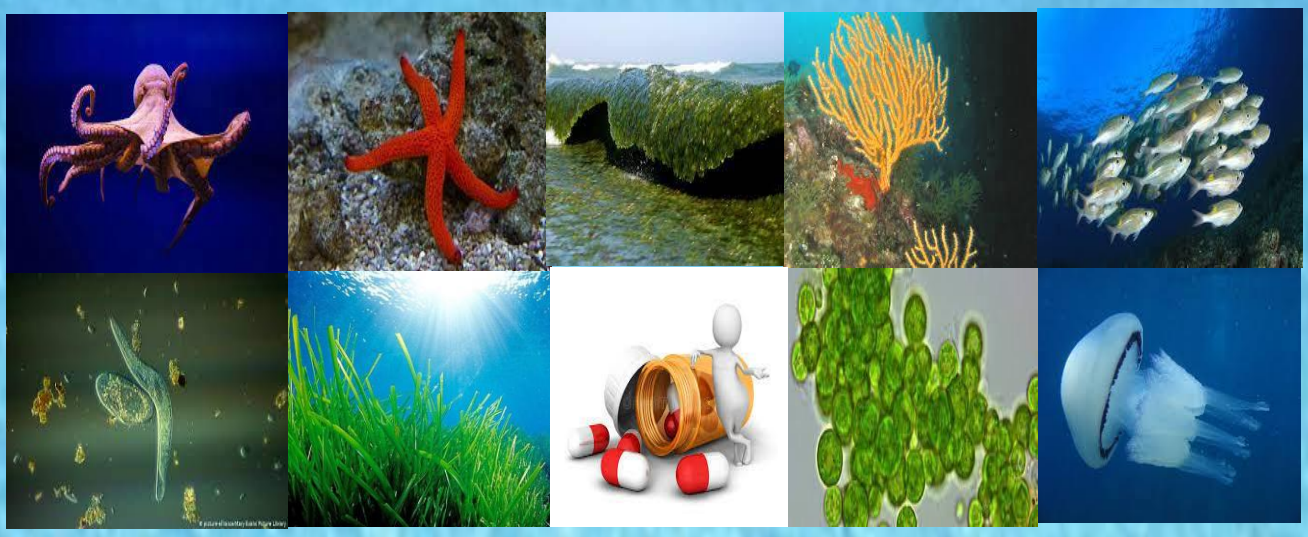

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BIO-BASED PRODUCTS FROM MEDITERRANEAN SEAWEEDS AND THEIR OPPORTUNITIES IN THE BIOECONOMY FIELD

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Seaweeds are attracting increasing attention as an alternative healthy food and renewable drug source and as agents of climate change mitigation that provide essential ecosystem services. In this context, seaweeds represent marine resources capable of supporting and pursuing the objectives of the Sustainable Blue Economy and the Bio-Based Circular Economy. In this context, we show the state of seaweed bio-based products and research on the Mediterranean Sea from the last 20 years. Results of this analysis show many investigations focusing on antimicrobial, antioxidant and anti-inflammatory activities. Although generally very limited, attempts at seaweed farming are present in Israel and some North African countries. Lastly, we focus on the Italian situation - including research, companies, and legislation on seaweed production - and discuss gaps, perspectives, and challenges for the potential development of a sustainable seaweed industry according to the Sustainable Blue Economy.

IN VITRO ANTI-INFLAMMATORY AND VASCULOPROTECTIVE EFFECTS OF RED CELL EXTRACT FROM THE BLACK SEA URCHIN *ARBACIA LIXULA*

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Sea urchins have emerged as an important source of bioactive compounds with anti-inflammatory and antioxidant properties relevant to human health. Since inflammation is a crucial pathogenic process in the development and progression of atherosclerosis, we here assessed the potential anti-inflammatory and vasculoprotective effects of coelomic red-cell methanolic extract of the black sea urchin *Arbacia lixula* in an in vitro model of endothelial cell dysfunction. Human microvascular endothelial cells (HMEC-1) were pretreated with *A. lixula* red-cell extract (10 and 100 μg/mL) before exposure to the pro-inflammatory cytokine tumor necrosis factor (TNF)-α. The extract was non-toxic after 24 h cell treatment and was characterized by antioxidant power and phenol content. The TNF-α-stimulated expression of adhesion molecules (VCAM-1, ICAM-1) and cytokines/chemokines (MCP-1, CCL-5, IL-6, IL-8, M-CSF) was significantly attenuated by *A. lixula* red-cell extract. This was functionally accompanied by a reduction in monocyte adhesion and chemotaxis towards activated endothelial cells. At the molecular level, the tested extract significantly counteracted the TNF-α-stimulated activation of the pro-inflammatory transcription factor NF-κB. These results provide evidence of potential anti-atherosclerotic properties of *A. lixula* red-cell extract, and open avenues in the discovery and development of dietary supplements and/or drugs for the prevention or treatment of cardiovascular diseases.

CEPHALOPODS AS SOURCE OF BIOACTIVE MOLECULES

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The marine environment is one of the main sources of bioactive compounds with biological and chemical diverse nature. A variety of marine organisms possess bioactive compounds with multifunctionalities that could have implications in physiological processes resulting in interesting for pharmaceutical research. Cephalopod mollusks have stimulated the scientific minds, artistic emotions and sensory palates of humans for millennia and coleoid cephalopods (squid, cuttlefish, and octopus) with complex nervous systems and sophisticated behaviors are also one of the commercially important invertebrates. Much research work has been done on the cephalopods, mainly about the feeding strategies: the salivary gland toxins, body and liver oils; the reproductive strategies: the ovarian-peptides, the nidamental gland products, accessory nidamental gland products and the associated symbiotic bacteria; the defense mechanisms: the ink glands and their bioactive products, the skin and mucus peptides, the hemolymph and the suckers peptides, squidvibrio association, the camouflage and reflectin-proteins. Here we will take into consideration: skin, ink, hemocytes, and suckers bioactive products mainly in *Sepia officinalis* and *Octopus vulgaris*.

DRUGS FROM THE SEA: THE BIOTECHNOLOGICAL POTENTIAL OF SPONGES

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Marine sponges, along with the sponge-associated microbiota, represent a remarkable source of compounds, exhibiting biotechnological activities as antiviral, anticancer, antifouling, antimicrobial, antifungal, antioxidant and antiaging. Sponges evolved a sophisticated system of chemical communications and defence, based on secondary metabolites, which preserve them against predation and microbial infections. For most sponge-derived bioactive compounds, it is not clear whether they are produced by the sponge itself, by the associated microorganisms, or by the interaction between sponges and associated microbial communities. In this study, we collected sponge samples off a wide range of Italian coasts. Each species was further extracted with solvents and chemical fractions were produced. The cytotoxic effect of sponge extracts and fractions was then evaluated by 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) assay. Our results showed cytotoxic activity against solid tumors, such as melanoma, mesothelioma, breast cancer, prostate cancer and pancreatic carcinoma. In addition, some extracts exhibited anti-inflammatory effects. A metataxonomic analysis was performed to define the bacterial communities associated to various sponges. Finally, a first attempt of setting-up small-scale integrated multi-trophic aquaculture (IMTA), considered as an environmental-friendly approach to produce sponge biomass, was tested for sponges that might lead to the production of compounds potentially useful for pharmacological, cosmeceutical, and nutraceutical applications.

MICROALGAE AS CELL FACTORIES: RESEARCH AND INDUSTRIAL APPLICATIONS

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The surge in demand for microalgae-based products, particularly in the nutraceutical and cosmetic markets, necessitates a continuous cycle of development and investments to meet demands effectively. The focal point of this PhD project revolves around the enhancement of an extract, derived from the diatom *P. tricornutum*, enriched with the carotenoid Fucoxanthin, renowned for its promises in various applications, including the treatment of diabetes, liver diseases, and lipid metabolism. Additionally, it exhibits substantial cosmeceutical properties, serving as an antioxidant, UV damage protector, and anti-wrinkle agent, thus encapsulating the characteristics of an innovative ingredient. To realize the full potential of Fucoxanthin, the development of a higher-yielding strain and an improved production method was studied, optimizing both biomass production within the photobioreactors and the extract itself. To gain a deeper understanding of the selected strain, a morphological study was conducted through electron microscopy. Following these laboratory phases, the strains were scaled up and grown in a closed photobioreactor within the production plant. Comprehensive analyses were conducted on the finished product, encompassing Fucoxanthin content, lipids, and the phytochemical profile of the extract.

PRE-CLINICAL INVESTIGATIONS: EFFECTS OF *PENNATULA PHOSPHOREA* IN AN *IN VITRO* MODEL OF SARCOPENIA

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Sarcopenia is a complex multifactorial condition characterized by the impairment of muscle components and functionality[1]. Current treatment strategies are unsatisfactory. The marine environment represents countless resources for the discovery of new for pharmacologically-active products[2]. In this study, we evaluated the protective potential of three *Pennatula phosphorea* extracts obtained from the fractionation with three different solvents: hexane, chloroform and methanol. All extracts were tested in an *in vitro* model of sarcopenia obtained treated C2C12, mouse skeletal myoblasts cells, with dexamethasone (DEX, 1μM, 48h). To select the non-cytotoxic concentrations, the extracts were tested at different concentrations (2.5-50 μg/ml) and MTT viability tests were performed. Informed by these results, we evaluated the protective activity of the extracts by testing them on DEX-treated C2C12 cells. This first analysis allowed us to identify the hexane extract as the most effective in preserve cells from DEX-induced mortality. Afterwards, through the cytofluorimetric (proliferation with CFSE) and immunofluorescence (myogenin positive cells %) analysis, we demonstrated that the hexane extract reduced the cell proliferation in favor of differentiation from myoblasts to myotubes. The same extract reduced the percentage of early apoptosis cells in an *in vitro* starvation-induced sarcopenia model.

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BIOACTIVE MOLECULES FROM CILIATES

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Ciliates are eukaryotic microorganisms living worldwide in every aquatic habitat, easy to perpetuate in the laboratory and expand into massive cultures. They synthesize a variety of structurally diverse bioactive molecules used to communicate socially, compete for habitat and food resources, and interact with prey and predators. Besides their native mechanisms and evolutionary correlations with signal molecules of multicellular organisms, ciliate bioactive molecules are attracting research attention for their potential utilization in medicine and pharmacology. One class of these molecules, described as 'pheromones', controls the cell self/not-self recognition phenomenon that ciliates manifest in switching from the growth stage to the sexual stage of their life cycle. The determination of the molecular structures of various pheromones (obtained in collaboration with Prof. K. Wüthrich, ETH, Zurich, and Dr. B. Pedrini, PSI, Villigen) in species of one of the evolutionarily most successful ciliates, *Euplotes*, has provided evidence that these proteins (alike mammalian cytokines and growth factors) rely on closely homologous structures to compete with one another to bind target cells in both autocrine (growth-promoting) and heterologous (sex-inducing) fashions. Assessed in heterologous cell systems for their mitotic activity, some pheromones have revealed surprising effects on human lymphocytes, thus suggesting to carefully inspect their potential use as immunomodulators.

VALORISATION OF AQUA FARMING EFFLUENT AS CULTURE MEDIUM FOR MICROALGAL BIOMASS PRODUCTION AND BIOACTIVE MOLECULES EXTRACTION

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Shrimp farming and recirculating aquaculture systems (RAS) generate nutrient-rich effluents that need to be treated before their release into the environment. Microalgae cultivation is emerging as a promising and eco-friendly approach to assimilate and transform the excess of nutrients in different wastewaters. This not only improves water quality but also holds potential for valuable algal biomass from which bioactive compounds, including vitamins, pigments, polyphenols, polyunsaturated fatty acids (PUFAs), polysaccharides, essential minerals, proteins and peptides, can be extracted [1-2]. The success of microalgae-based remediation relies on selecting robust, high-production microalgae strains capable of thriving in the complex composition of recirculating aquaculture system wastewaters. The integration of photobioreactors in the farming facilities, further enhances the efficiency of microalgae-based wastewater treatment by providing a controlled environment for optimal growth. The BIORAS_SHRIMP (www.bioras-shrimp.eu) project mainly focusing on new shrimp aquaculture systems based on a circular economy perspective, offers an opportunity also for the microalgal-based industries. One of the aims of the project is, in fact, the investigation of the improvement of the health promoting effects of extracts/compounds from selected microalgae species (*Chlorella vulgaris*, *Phaeodactylum tricornutum*, *Porphyridium purpureum*, *Nannochloropsis oculata*, *Scenedesmus sp*., *Arthrospira maxima*, *Tetraselmis chuii*), cultured on shrimp aquaculture wastewaters under innovative conditions.

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DIATOMS: THERAPEUTIC POTENTIAL AND APPLICATIONS OF METABOLITES FROM THE SEA

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Diatoms are microalgae playing important roles in the biogeochemical circulation of silica, nitrogen, and carbon, characterized by fast turnover and high yields. They are quite rich in several secondary metabolites, including saturated and unsaturated fatty acids, esters, sterols, acyl lipids, proteins, and flavonoids. In addition, the bioactive compounds contained in diatoms were reported to be potential anti-cancer, anti-oxidant and anti-bacterial agents. Chemical ecology approaches help understanding their physiological roles and identifying possible applications. Several diatoms showed anti-mitotic and anti-proliferative activities. Remarkably, diatoms of the genus *Cocconeis*, known to induce sex reversal in some marine shrimps, demonstrated a noteworthy cell-death activity against human solid tumors. This activity is due to a still unknown small fatty acid and it proceeds through ferroptosis, being characterized by high specificity. The same diatoms, when cultivated in opportune conditions, exhibit antibacterial activity and in this case the responsible compounds have not yet been characterized. Finally, it is known that lysophosphatidylcholines and pheophorbide a (a breakdown product of chlorophyll), are responsible for various anti-inflammatory activities. For all these reasons, we investigate the ecological relationships of marine diatoms with their grazers and test the activity of extracts and fractions on model invertebrates and human cell lines.

Phycocyanin Production by *Arthrospira platensis* Under Mixotrophic Conditions.

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Microalgae represent a natural reservoir of diverse biologically active compounds, including vitamins, pigments, and fatty acids. Furthermore, microalgae are recognized for their notable antioxidant, immune-stimulant, antiviral, and antibiotic effects. The therapeutic properties of *Spirulina* extracts, such as phycobiliproteins (e.g., phycocyanin), have been demonstrated in terms of anticancer and anti-inflammatory effects. This study explores the mixotrophic cultivation of *Spirulina* using cheese whey (CW), rich in organic source, as a sustainable substrate. Mixotrophic cultures exhibited faster growth, suggesting potential for quick biomass production. Under mixotrophy, *Spirulina* produces significantly more phycocyanin than in photoautotrophic conditions (3.52 mg mL^{-1} vs. 2.55 mg mL^{-1}), highlighting that CW's can boost the metabolic pathways leading to the synthesis of this relevant antioxidant, which could be sold in the market at relatively high prices. The fatty acid methyl esters profile of *S. platensis* under mixotrophy resembled that of olive oil with essential monounsaturated fatty acids. The study emphasizes the need to keep CW supplementation below 2.5% v v^{-1} for optimal nutritional and health benefits, including preventing endothelial dysfunctions and cardiovascular deseases in general.

EFFECTS OF A HYDROALCOHOLIC EXTRACT FROM CYMODOCEA NODOSA ON THE METABOLIC PROFILE IN OBESOGENIC DIET-FED MICE

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The metabolic syndrome is a multifactorial pathology that predisposes to the onset of other diseases, including obesity, cardiovascular pathologies and type 2 diabetes mellitus. This scenario shares a close connection with the alterations of the different adipocyte phenotypes that regulate metabolic homeostasis[1].

Cymodocea nodosa (Ucria) Asch., a dioecious marine angiosperm, represents a possible phytotherapeutic/nutraceutical option for the management of metabolic disorders[2]. The leaf hydroalcoholic extract of *Cymodocea nodosa* (CYMextract) collected in the Ligurian Sea (Italy), rich in flavonoids and phenolic acids (titled in chicoric acid), was tested in a murine model of cardiometabolic disorder induced by high fat diet for 9 weeks (CYMextract dosage of 500 mg/kg/day).

The results obtained show how CYMextract has an interesting effect in limiting the increase in body weight induced by an obesogenic diet and promoting the thermogenically active adipocyte phenotype.

Weight changes of different tissues (visceral white adipose tissue, brown adipose tissue, perithymic adipose tissue, whole heart and left ventricle) as well as positive modulation of the glycemic profile and specific molecular markers (irisin and citrate synthase) emerged.

CYMextract also showed a positive effect on the prevention of metabolic activity and hypertrophic processes at cardiac level.

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MARINE POLYKETIDES AS A PROMISING STRATEGY TO FIGHT CANCER

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Marine sponges represent one of the richest sources of natural marine compounds with anticancer potential. The aim of the study was to assess the cytotoxic effects induced by smenamide A, a peptide-polyketide, and smenolactone D, a polyketide, isolated from the Caribbean marine sponge *Smenospongia aurea*. Their anticancer potential was tested on a panel of human cancer cell lines representing solid and hematological tumors. Smenamide-A (1 nM-20 μM) did not exhibit cytotoxic effects in any tested cell lines. In contrast, smenolactone-D (1-10 μM) decreased cell viability in a concentration-dependent manner in all the tested cells. Leukemia Jurkat cells resulted the most sensitive, thus, subsequent experiments were conducted on this cell line. In particular, we investigated the mechanism of cell death induced by smenolactone-D. The obtained results suggest that the cytotoxicity triggered by smenolactone-D relies on a combined mechanism of action involving apoptosis and a non-canonical form of cell death, i.e. ferroptosis. In light of the issues associated with the development of resistance to anticancer therapy based on apoptosis induction, this multifaceted mechanism is a favorable aspect and makes smenolactone-D a promising lead compound for the management of diseases such as cancer.

HALOPHYTE PLANTS: ENVIRONMENTALLY FRIENDLY AND HUMAN HEALTHY

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Halophytes can survive in highly saline soils; the optimal salinity for the growth of most halophytes ranges from 50 to 250 mM NaCl, and species such as *Salicornia* spp. can grow and produce as much as conventional crops even when irrigated with seawater. For these reasons, halophytes play a role in coastal-area preservation and represent valuable scientific models for investigating salt-tolerance mechanisms, their exploitation as food and non-food crops could be a winning strategy in a salinising world.
Along the species found in the Mediterranean area, *Salicornia perennans, Beta vulgaris subsp. maritima* and *Crithmum maritimum* are also interesting for human nutrition. These can be potential resources, such as new or relatively new vegetable crops, to produce raw or minimally processed (or ready-to-eat) products, considering their nutritional properties and nutraceuticals. The edible parts of these species are appreciated due to their salty taste and high content of antioxidant compounds and essential nutrients (minerals, vitamins and amino acids). The fennel-like scent of *C. maritimum* (sea fennel) leaves makes it suitable for an aromatic powder for flavouring food. However, their consumption is allowed according to the recommended daily intake regulation because of the sodium and/or oxalate concentration.

STRUCTURAL CHARACTERIZATION, AND *IN VITRO* PROINFLAMMATORY AND ANTIPROLIFERATIVE ACTIVITY OF POLYSACCHARIDES FROM *SPIRULINA PLATENSIS*

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Inflammation plays a critical role in cellular damage, activating mechanisms that can induce apoptosis and subsequent cell death.
In this context, microalgae represent a promising source of bioactive compounds, also recognized for their anti-cancer properties. In recent years, particular attention has been paid to polysaccharides derived from microalgae, that have shown to possess various activities including efficacy against tumors.
In this study, we isolated polysaccharides, named SSG8, from *Spirulina Platensis* and characterized them by assessing the content of monosaccharides, proteins, and sulfate groups. Then, we evaluated their potential antitumor effect in a human cell line of non-small cell lung cancer (A549). Data showed that SSG8 exhibited a dose-dependent cytotoxic effect, with an IC_{50} value of 220 µg/ml. The role played by the apoptotic process in the SSG8-induced cytotoxicity was evaluated by measuring internucleosomal DNA fragmentation after 24 h of SSG8 treatment. A marked pro-inflammatory effect, associated to a significant release of TNFα, IL6 and IL21, was also observed in A549 cells after treatment with SSG8 at 150 µg/ml for 24 h. To investigate in more detail, the anti-tumor activity of SSG8 the transcriptional expression of pro-apoptotic (i.e. BAX, BCL2, and SURVIVIN) and pro-inflammatory (i.e. COX2, ACE2, TNFα, IL6, and NFKB) genes was also assessed in A549 cells.

The marine world as a source of promising molecules for the treatment of cardiac amyloidosis

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Amyloidoses are a group of diseases characterized by the abnormal accumulation, in the extracellular area, of insoluble misfolded protein aggregates commonly called amyloid fibrils. Transthyretin amyloidoses (ATTRs) are classified in: senile systemic amyloidosis (SSA) related to wild-type TTR (wt-TTR); familial amyloid cardiomyopathy (FAC) and familial amyloid polyneuropathy (FAP) caused by TTR mutants. While SSA and FAC stand out by fibril deposit formation mainly in the heart, FAP is characterized by the accumulation of fibrils in peripheral and autonomic nerves, heart but also in the lung, gut and carpal tunnel.
Physiologically, TTR is a homotetrameric carried protein that contributes to the transport of the thyroxine (T_4) and, to the retinol through the binding with retinol binding protein (RBP).
TTR possesses an intrinsic amyloidogenic potential related to its high level of the β strand. Under pathological conditions, TTR undergoes a misfolding process that leads to the formation of protein aggregates and fibrils in the tissues leading to organ damage and dysfunction, inducing amyloidosis disease onset.
One therapeutic strategy to contrast the tetramer dissociation is to use molecules able to bind the TTR contrasting the tetramer dissociation. Among the several natural molecules, some derived from marine world. Here, we report the recent finding about the positive effect that some compounds or extract have on the tetramer stabilization.

STUDY OF THE VIRUCIDAL EFFECTS OF MICROALGAE-EXTRACTED POLYSACCHARIDES AND MOLECULES PRODUCED BY AQUATIC CILIATES

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The study of natural compounds' impact on viral viability is essential for developing sustainable alternatives to synthetic chemicals. Molecules produced by cyanobacteria, such as *Climacostomum virens* and *Arthrospira platensis*, could be useful for this aim. *C. virens* produces a toxin called climacostol, which has demonstrated biological activity against bacterial and fungal pathogens, protozoa, human and animal cell, and isolated mitochondria. *A. platensis*, on the other hand, produces polysaccharides (SPPs) with antiviral activities against enveloped viruses. This study separately evaluated in vitro the effects of climacostol and SPPs on Human Adenovirus 5 (HAdV5), highly stable pathogenic virus known for persistence in environment and resistance to disinfection. Various viral titers of HAdV5 were exposed to a concentration of $2 \cdot 10^3$ µg/ml of climacostol, resulted to toxic for cell culture, for 30 minutes. The results showed a 99.9% reduction in viral titer, indicating high sensitivity of HAdV5. For SPPs the no toxic concentration of 84.37 µg/ml was tested at 15, 30, 60 minutes, resulting in an average titer reduction of 98%-99%, independent of contact time. These preliminary data suggest that climacostol and SPPs have significant antiviral properties, necessitating further investigations into their mechanisms of action.

Relatori (in ordine alfabetico) e presentazioni

Armeli Minicante Simona (CNR-ISMAR Venezia)
Bio-based products from Mediterranean seaweeds and their opportunities in the bioeconomy field
Banti Matteo (Dipartimento di Farmacia, UNIPI)
Structural characterization and in vitro pro-inflammatory and antiproliferative activity of polysaccharides from Spirulina platensis
Ciccone Lidia (Dipartimento di Farmacia, UNIPI)
The marine world as a source of promising molecules for the treatment of cardiac amyloidosis
Costantini Maria (Stazione Anton Dohrn, Napoli)
Drugs from the sea: the biotechnological potential of sponges
Di Cosmo Anna (Dipartimento di Biologia, UNINA)
Cephalopods as source of bioactive molecules
Flori Lorenzo (Dipartimento di Farmacia, UNIPI)
Effects of a hydroalcoholic extract from Cymodocea nodosa on the metabolic profile in obesogenic diet-fed mice.
Lionti Joseph (Dipartimento di Med. Sperimentale (DIMES), UNIGE)
Microalgae as cell factories: research and industrial applications
Lutzu Gianni (R&D Teregroup S.r.l., Modena)
Phycocianin production by Arthrospira platensis under mixotrophic conditions
Pagani Alessandra (Dipartimento di Biologia, UNIPI)
Study of the virucidal effects of microalgae-extracted polysaccharides and molecules produced by aquatic ciliates
Pistelli Laura (Dipartimento DISAAA, UNIPI)
Halophyte plants: environmental friendly and human healthy
Scoditti Egeria (Istituto di Fisiologia clinica, CNR Lecce)
In vitro anti-inflammatory and vasculoprotective effects of red cell extract from the Black Sea urchin *Arbacia lixula*
Turrini Eleonora (Dipartimento di Scienze per la Qualità della Vita, UNIBO)
Marine polyketides as a promising strategy to fight cancer
Vallesi Adriana (Scuola di Bioscienze e Medicina veterinaria, UNICAM)
Bioactive molecules from ciliate protists
Venturi Daniel (Dipartimento NEUROFARBA, UNIFI)
Pre-clinical investigations: effects of Pennatula phosphorea in an in vitro model of sarcopenia
Zonno Vincenzo (Dipartimento DISTeBA, Unisalento)
Valorization of aqua farming effluent as culture medium for microalgal biomass production and bioactive molecules extraction.
Zupo Valerio (Stazione Anton Dohrn, Napoli)
Diatoms: therapeutic potential and applications of metabolites from the sea

Elenco dei Moderatori (in ordine alfabetico)

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