VECTORS of Change in Oceans and Seas Marine Life, Impact on Economic Sectors

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VECTORS Overview

'VECTORS seeks to develop integrated, multidisciplinary research-based understanding that will contribute the information and knowledge required for addressing forthcoming requirements, policies and regulations across multiple sectors.'

Marine life makes a substantial contribution to the economy and society of Europe. In reflection of this VECTORS is a substantial integrated EU funded project of 38 partner institutes and a budget of €16.33 million. It aims to elucidate the drivers, pressures and vectors that cause change in marine life, the mechanisms by which they do so, the impacts that they have on ecosystem structures and functioning, and on the economics of associated marine sectors and society. VECTORS will particularly focus on causes and consequences of invasive alien species, outbreak forming species, and changes in fish distribution and productivity. New and existing knowledge and insight will be synthesized and integrated to project changes in marine life, ecosystems and economies under future scenarios for adaptation and mitigation in the light of new technologies, fishing strategies and policy needs. VECTORS will evaluate current forms and mechanisms of marine governance in relation to the vectors of change. Based on its findings, VECTORS will provide solutions and tools for relevant stakeholders and policymakers, to be available for use during the lifetime of the project.

The project will address a complex array of interests comprising areas of concern for marine life, biodiversity, sectoral interests, regional seas, and academic disciplines and especially the interests of stakeholders. VECTORS will ensure that the links and interactions between all these areas of interest are explored, explained, modelled and communicated effectively to the relevant stakeholders. The VECTORS consortium is extremely experienced and genuinely multidisciplinary. It includes a mixture of natural scientists with knowledge of socio-economic aspects, and social scientists (environmental economists, policy and governance analysts and environmental law specialists) with interests in natural system functioning. VECTORS is therefore fully equipped to deliver the integrated interdisciplinary research required to achieve its objectives with maximal impact in the arenas of science, policy, management and society.

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Executive Summary

The marine environment has been recognized as a rich source of bioactive metabolites with various biological and pharmacological activities. The chemical complexity and biological diversity of the marine-derived compounds is enormous, so that bioprospecting of marine organisms today represents a major tool for the discovery of new therapeutic agents and drug candidates.

On a global scale, jellyfish populations in coastal marine ecosystems exhibit increasing trends of abundance. High-density outbreaks may directly or indirectly negatively affect human economic and recreational activities, as well as public health. Conversely, with a positive perspective, the large amount of jellyfish biomass could be considered to be a valuable source of bioactive compounds beneficial for humans, including bioactive peptides, collagen and gelatine, oligosaccharides, fatty acids, enzymes, calcium, water-soluble minerals, and biopolymers. The various identified biological activities, including antioxidant activity, make them a potentially valuable material for food, cosmetic, and biomedical industries, such as has been proposed for seafood processing by-products

As interest in the biology of marine jellyfish grows, a number of jellyfish metabolites with potential health benefits, such as anticancer or antioxidant activities, are increasingly reported. VECTORS has created the World Jellyfish Patents (WJP) database which collates available information on international patents on jellyfish utilization in different fields, such as biological applications, cooking treatments and recipes, pharmacological and cosmetic uses.

Introduction

Marine bioprospecting deals with the search for useful organic compounds in marine biodiversity as new resources for pharmacology, cosmetics, nutritional and energetic applications. In the last 50 years, more than 10,000 scientific articles have described new marine natural products (Abida et al. 2013), with about 18,000 products reported from fewer than 5,000 surveyed marine species (Global Ocean Commission, 2013) and the number of natural products is growing at a rate of 4% per year (Arrieta et al. 2010). An exponential growth has been recorded in recent years largely due to technological advancements. Several bioactive extracts and purified molecules have been recognized and patented from marine benthic and planktonic organisms, whose large taxonomic and functional diversity, from mega-benthos and mega-plankton to viruses, underlies a vast and largely unexplored repository of bioactive molecules of interest to humans (Fig. 1). The discovery of organisms containing bioactive molecules or genes of commercial interest now parallels the overall interest for exploration of marine biodiversity. The percentage of described marine eukaryotic species being a source of commercial patents (BOX 1) is more than twice the percentage of terrestrial species, with a predicted success rate in finding previously undescribed bioactive compounds 500 times higher in marine organisms than that for terrestrial species (Venugopal 2008).

The aim of WP3.2 is to understand the potential societal impacts of changes in the marine environment through the assessment of ecosystem services. In this deliverable, the focus is specifically on invasive alien species and outbreak forming species, two of the main drivers of change investigated in VECTORS. As well as understanding the potential negative implications, VECTORS seeks to consider possible mitigation measures and opportunities for positive applications that benefit human societies. The WJP database that this deliverable describes, is a VECTORS product that highlights the potential for fostering management practices that not only help to control jellyfish outbreaks, which can be detrimental to the marine environment and society, but also make use of jellyfish for societal gains.

The present report aims to compile the first available inventory of patents dealing with jellyfish applications in different fields. Patents range from those relating to gelatinous biomass harvesting and exploitation as food or feed, to the discovery of new biomaterials and biomolecules for medicine and cosmetics, to the development of mitigation and protection tools against jellyfish stings. This information demonstrates the potential role that jellyfish could have in contributing to marine provisioning ecosystem services (i.e. food stuffs and raw materials).

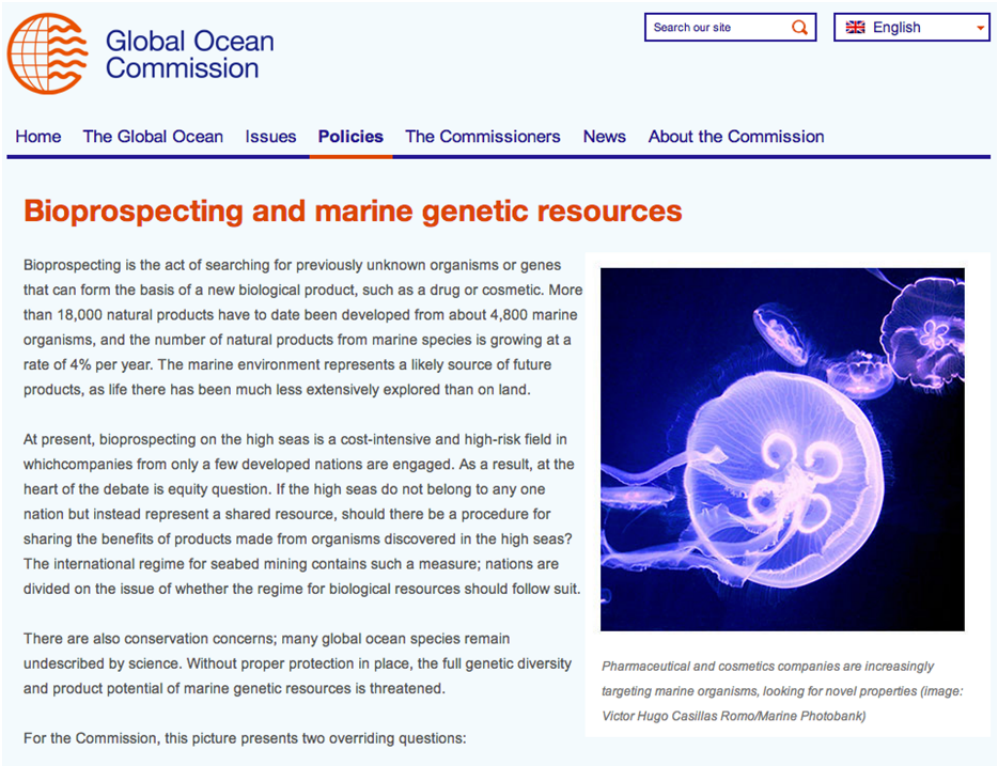

Fig. 1. The bioprospecting website of the Global Ocean Commission (http://www.globaloceancommission.org/policies/bioprospecting-and-marine-genetic-resources/). Jellyfish are regarded as key target organisms in the search for new bioactive compounds.

BOX 1 - What is a patent? (source: http://www.wipo.int/patents/en)

A patent is an exclusive right granted for an invention, which is a product or a process that provides, in general, a new way of doing something, or offers a new technical solution to a problem. To get a patent, technical information about the invention must be disclosed to the public in a patent application.
In principle, the patent owner has the exclusive right to prevent or stop others from commercially exploiting the patented invention. In other words, patent protection means that the invention cannot be commercially made, used, distributed, imported or sold by others without the patent owner's consent.
Patents are territorial rights. In general, the exclusive rights are only applicable in the country or region in which a patent has been filed and granted, in accordance with the law of that country or region. The protection is granted for a limited period, generally 20 years from the filing date of the application.

The exponentially increasing rate in filing of patents and patent applications associated with marine organisms is largely due to recent technological advances in exploring the ocean and its diversity. The chemical, biological and ecological diversity of marine metabolites has also contributed to the discovery of potent compounds with strong antitumor activities. However, their structural diversity, from simple linear peptides to complex macrocyclic polyethers, represents one of the first difficulties in new drug discovery from marine natural products. Recent advances in sophisticated technologies for the isolation and characterization of marine natural products and the development of high-throughput screening methods have substantially increased the rate of discovery of various compounds with biomedical applications. High-throughput screening, combinatorial chemistry and, most recently, *in silico* virtual screening techniques partly supported successful attempts to identify new drug candidates. However, the classical approach to recognize bioactive compounds through analysis of their specific biologic activity remains highly effective, especially when associated with the above-mentioned technological approaches (Leone et al. 2013).

The same advancement allowed acceleration of our capacities to explore abundant but neglected resources, such as cnidarian jellyfish. On a global scale, jellyfish populations in coastal marine ecosystems exhibit increasing trends of abundance, which may directly or indirectly negatively affect human economic and recreational activities, as well as public health. They are therefore becoming a crucial ecological and societal issue in recent decades (Brotz et al. 2012; Boero 2013). Jellyfish outbreaks increasingly interfere with human economic and recreational activities, such as bathing, fishery, tourism, as well as public health, and coincide with human proliferations and environmental perturbations (Purcell 2012). Jellyfish have been reported to clog fishing nets, spoil commercial catches, cause serious damage to aquaculture, clog the cooling systems of coastal power plants, and harm or even kill professional and recreational water users [Purcell et al. 2007; Boero et al. 2008).

Conversely, the large amount of jellyfish biomass could be considered to be a valuable source of bioactive compounds beneficial to humans, including bioactive peptides, collagen and gelatine, oligosaccharides, fatty acids, enzymes, calcium, water-soluble minerals, and biopolymers. The numerous identified biological activities, including antioxidant activities, make them a potentially valuable material for food, cosmetic, and biomedical industries, such as has been proposed for seafood processing by-products. As predicted by Purcell (2012): "…*with high populations of jellyfish, interest in new commercial products will increase. Additional species suitable for human food and animal feeds, as well as for new uses in medicine and biotechnology, could be utilized*".

Indeed, cnidarian polyps and jellyfish have increasingly become an attractive source of physiologically active compounds. Extracts from different species were reported to exert cytotoxic and hemolytic effects (Kang et al. 2009), or insecticidal (Yu et al. 2005), cardiovascular (Ramasamy et al. 2005), antioxidant (Yu et al. 2005), anti-microbial (Ovchinnikova et al. 2006) activities. Strong fibrinogenolytic factors have recently been found in the moon jellyfish *Aurelia aurita* tentacle extract (Rastogi et al. 2012). Partially purified venom from the mauve stinger jellyfish *Pelagia noctiluca* displayed potent anti-tumoral properties against U87 glioblastoma cells (Ayed et al. 2012). Collagen hydrolysate from the edible jellyfish *Rhopilema esculentum* exerted antioxidant and protective effects on mice skin subjected to photo aging induced by UV irradiation (Zhuang et al. 2009). Collagen from the giant jellyfish *Nemopilema nomurai* was shown to exert an immunostimulatory effect on the hybridoma cell line HB4C5 and human peripheral blood lymphocytes (Sugahara et al. 2006; Nishimoto et al. 2008; Morishige et al. 2011). Clearly, several jellyfish metabolites with healthful potential, such as anticancer or antioxidant activities, are increasingly reported and patented, and the interest in bioprospecting jellyfish is likely to grow in future years, leading to new resources for humans and new ways to address a number of current global issues.

A research area that has the potential for considerable human benefit and would help support basic jellyfish research is investigation of the efficacy of many traditional medicinal uses of jellyfish. Jellyfish have been used to alleviate, cure or improve an array of ailments, including arthritis, bronchitis, burns, fatigue, gout, hypertension, menstruation pain and ulcers. Recent studies have confirmed that jellyfish collagen suppresses arthritis in laboratory rats (Hsieh 2001) and stimulates autoimmune and inflammatory responses in humans (Sugahara et al. 2006).

Jellyfish as a food source

Jellyfish have been eaten by humans since 300 AD in China, being considered an ideal natural food source. Indeed, their fresh tissues are at the same time extremely low in fats, cholesterol, sugars and consequently in calories, but rich in proteins, polyunsatured fatty acids, and other metabolites with valuable anti-oxidant and bioactivite properties (Hsieh et al, 2001; Leone et al 2013). . However, only recently jellyfish aquaculture has become a commercial industry, with an increasing demand of ready-to-eat products in most of East and Southeast Asian countries (Purcell et al. 2013). Between 1996 and 2005, 425,000 tonnes per year were estimated to be globally harvested for human consumption in Southeast Asia (FAO 1999). Currently, jellyfish fisheries exist in 15 countries, including China, India, Indonesia, Japan, Malaysia and the Philippines, with a few export industries in Australia and the USA. The jellyfish product is regarded as a high-quality seafood alternative that can be sprinkled on salads for extra crunch, prepared as a seafood salad, or displayed on sushi bars. Although so far shunned in

Western countries, the fact that jellyfish represent a low calorie seafood product, with the potential of providing a number of health benefits, suggests that it will eventually be welcomed by many European countries (Hsieh 2001).

Many patents are about the preparation of jellyfish for food processing (storage, conservation, and preparation). If jellyfish harvesting is designed for commerce, preservation represents a key step of jellyfish treatment because it allows the storage of jellyfish over time. Since 1997, as reported in the European Patent Office, several inventions describe the treatments of jellyfish with salt and alum (aluminium sulphate): this is the technique most used in Asia to obtain antimicrobial preservation and creates a product good in crispness and taste (see Jellyfish Database Excel File – Annex 1: CN101502277; CN1214205; CN1154205; JPH09121816). Another technique used for jellyfish preservation is based on the extraction of garden balsam (*Impatiens balsamina*) with alcohol (JPH10150954). The use of this balsam is proposed as a storage protocol to dry jellyfish tissues by means of natural additive versus the use of a chemical additive (usually potassium alum, a hydrated form of potassium aluminium sulfate).

Before serving, it is mandatory to remove the salt and alum from the preserved jellyfish. Different techniques are patented for the removal of the alum through high-pressure treatment (CN101301096) or with citric acid, which eliminates different chemical combinations of aluminium in the preserved jellyfish tissues (CN103300263). Once the aluminium has been removed, patents have been obtained for food preparation protocols (e.g. cooking in hot oil with the addition of herbs, ginger or other ingredients CN101411481, CN101396147; combined with other sea food, such as holothurians, CN101053399; or cooked in boiling water, seasoned with oil and vinegar and stored in sterile bags for short-term consumption, CN101411520).

Jellyfish as a source of collagen

Many jellyfish patents also deal with collagen because of its worldwide use in cosmetics and pharmaceuticals. It is usually obtained from cattle hides, pork skins, or connective tissues from various animals, and it is usually extracted as soluble collagen. However, collagen sources from animals carry with them the possibilities of infection with viral diseases such as BSE (or mad cow disease), foot and mouth disease, hog cholera, avian flu and others. Blood and fat must be removed from the tissues of source vertebrates, exposing the workers to the risk of infection and diseases, and resulting in relatively high costs. Collagen from jellyfish is not subject to infection from common vertebrate diseases. Jellyfish are relatively easy to clean, and do not require depilation, blood or fat removal. The abundance of collagen, proteins and other bio-molecules make jellyfish a valuable source of great commercial potential for nutraceutics, cosmetics and pharmacopeia, assuming they may help the increasing aging population by preventing or treating lifestyle-related diseases.

Extracted collagen can have several uses in cosmetic and in pharmaceutical fields. Jellyfish collagen can be used as a wound dressing (US2010285102), in the treatment of rheumatoid arthritis (US6894029), and to repair a barrier function of a dead skin cell (KR20130048164). Thus, many patents are also dedicated to improving collagen extraction by different methods:

- by isolating jellyfish collagen through sequential acid extraction, centrifugation and saline precipitation (WO9517428);
- by freezing jellyfish at -20°C, thawing the jellyfish to obtain about 4% of the solid content and then separating water-soluble protein from the solid content (JP2003321497);
- by digestion of shredded jellyfish with buffer solutions of pH ranging from 6.0 to 8.0 (JP2004099513);
- by using an overall acid process (CN102924591);
- by warming jellyfish tissues followed by desalination, concentration and drying (CN101245095);
- by endogenous enzymatic decomposition (JP2007051191).

Applications for medicine

As previously mentioned, jellyfish are renowned in Asian countries for their nutraceutical and medical properties. Jellyfish bio-molecules are used in the treatment of several diseases such as diabetes, AIDS, Alzheimers, and hypertension. A recent U.S. patent No. 7671015 from Quincy Bioscience, a research-based biotechnology company, covers the use of aequorin-containing compounds for the prevention and alleviation of symptoms related to calcium imbalance. Calcium is fundamental for proper neuron function. In human-based trials, aequorin was effective at improving aspects of cognition such as spatial working memory and executive function. The pharmaceutical product, named *Prevagen* (http://www.prevagen.com), is now commercially available (Fig. 2). Other patents report jellyfish compounds are beneficial to protect against hypertension (CN1306777, CN 101862375, CN102409072, CN101422195, CN101669659).

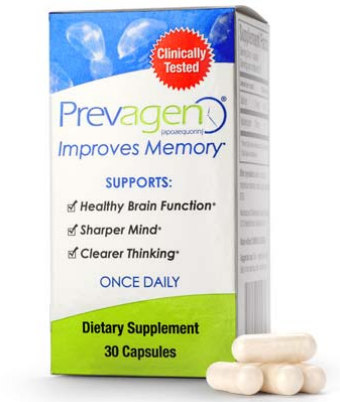

Fig. 2. Prevagen® (apoaequorin from the hydrozoan jellyfish Aequorea victoria found in Puget Sound, USA) has been clinically shown to help with mild memory problems associated with aging.

Other uses

Jellyfish patents have also been developed in other fields of application. For instance, the high demand for jellyfish in Asia produced several patented aquaculture techniques including methods for jellyfish reproduction, induced and optimized by a chemical reagent (CN101933483), or for extending jellyfish life span and improving jellyfish spawning and fertilization rates (CN101965809).

A key biomedical application of jellyfish biomolecules deals with Fluorescent Proteins (FPs): among them, the *Aequorea victoria* Green FP is the most characterized and best understood fluorescent protein. Wild type GFP derives from jellyfish living in North Pacific areas. The 2008 Nobel Prize in Chemistry was awarded for the discovery and development of the green fluorescent protein (Shimomura et al. 1962; Chalfie et al. 1994; Heim et al. 1995) with a number of applications in drug discovery research, medicine and biological sciences. The introduction of certain folding mutations improves the yield of correctly folded GFP molecules at 37°C. Red-shift mutations are also required to enable the fluorescence to be measured by standard laboratory fluorescence detection instruments. GFP can be used as a reporter molecule to build up a detailed picture of the distribution, trafficking and function of proteins within cells and to evaluate how drug candidates affect these processes in a cellular environment. A number of patents in Europe and USA claim these mutations, which are now pooled in patent portfolios held by international biotechnology companies, such as by Amersham Biosciences (US 5625048, US 5777079, US 5804387 US 5968738 US 5994077 US 6054321 US 6066476 US 6077707 US 6090919 US 6124128 US 6172188 EP 851874 EP0804457). The GFP discovery now sustains a wide biotechnological market, and new patents are continuously released following development of novel molecular adaptations improving FP applicability (e.g., WO2012063897, mutation of GFP in order to change its fluorescence according to the different pressure present in a liquid).

More as a historical curiosity than for its scientific interest, a patent released in 1970 (US3524276A) is also listed therein, dealing with an acoustic method for the "elimination" of jellyfish from surface waters (with untested efficacy). Forty-three years later, a new patent (KR10-1317021) deals with the design and implementation of an autonomous jellyfish removal robot system, called JEROS, to clear waters in sensitive coastal areas affected by jellyfish swarms that may clog the cooling systems of coastal industries and power plants.

More generally, jellyfish are now regarded as a key taxon for the production of large amounts of nutraceutical and pharmaceutical components that are particularly interesting for their possible therapeutic uses (Mariottini and Pane 2014) and to support highly rewarding mining for new molecules.

The WJD Database

The WJD database (see **Jellyfish Database Excel File** – Annex 1) includes information on 116 jellyfish-related patents mostly issued in the last 20 years (1993-2013) by national and international patent offices, such as the World Intellectual Property Organization (WIPO), the European Patent Office (EPO), or national ones, such as the US Patent Office, the Chinese Patent Office (SIPO), or the Korean Intellectual Property Office (KIPO).

The database is collated within a searchable Excel file where patents are listed according to the following categories:

- id database number (A column)
- patent number (B column)
- Country
- International Patent Classification (IPC) Official Publication
- Patent name
- Date of publication
- Inventor
- Methods (short description)
- Field of applicability
- Source organism
- Original document (pdf)
- Reference (internet link)

Out of the total 116 patents, 65 were issued in China (CN), 17 in Japan (JP), 13 in the USA (US), 8 in Korea (KR), 8 in Europe (EP), 1 in Russia (RU). The remaining 4 patents (WO) were directly released by World Intellectual Property Organization, the global forum for intellectual property services, policy, information and cooperation established in 1967 as a self-funding agency of the United Nations, with 186 member states.

The following fields of applicability are identified as follows:

- food industry and nutraceutics (51)
- pharmaceutics and cosmetics (43)
- applied biology and diagnostic methods (12)
- aquaculture (5)
- agriculture (3)
- coastal management (2)

Additional information for each patent is provided as a pdf document that can automatically be opened through a hypertext link (column K) within the Excel file. All pdf documents are contained in a folder named **Jellyfish patent supplementary information**, representing an integral part of this deliverable.

The database is open access and can be downloaded from the VECTORS website. Following the conclusion of the VECTORS project in 2015, the database will be maintained and updated by CONISMA in the framework of jellyfish-related research programmes. It is intended as a tool to encourage the future development of innovations and new technologies in every field of jellyfish-based research.

Conclusion

Jellyfish outbreaks are known to negatively impact human society through many direct and indirect means, as discussed in this report. VECTORS is studying these aspects to try to understand the potential consequences and mitigation opportunities for the future with the aim of informing future management and governance. However, there are potentially positive outcomes that need equal attention. The WJP database has been produced as a VECTORS product to collate existing information on jellyfish patents in order to facilitate future investigation, and hopefully use, of jellyfish for societal benefits. It highlights the many benefits that jellyfish may have to offer society.

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