escola superior de turismo
e tecnologia do mar
instituto politécnico de leiria

Invasive Marine Macroalgae and their Current and Potential Use in Cosmetics

Colin McReynolds

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Title: Invasive Marine Macroalgae and their Current and Potential Use in Cosmetics.

Título: Macroalgas invasoras marinhas e o seu potencial atual e futuro, na cosmética.

Abstract

With increasing interconnectivity, human population growth along coastlines and changing climate, nearshore ecological assemblages are being modified at an unprecedented rate. These changes are bringing to light widespread proliferations of macroalgae, with various effects on the affected ecosystems. However, this abundance may also present opportunities. The production of cosmetics, and particularly those from natural origin, is in high demand. Many of the invasive species have demonstrated biological activity that can be applied to skin care products, so-called 'cosmeceuticals'. A survey of common 'invasive' species revealed 47 species, 16 Chlorophyta, 19 Rhodophyta and 12 Phaeophyta. Their effects are interlinked but the most commonly recorded effect was habitat change, followed change of ecosystem processes, and finally genetic effects. Economic effects are difficult to quantify, containment and/or early eradication are the most effective. Re-using algae from containment programs could help finance these operations, or be an added incentive for their harvest. A literature review was from performed total of 198 articles on the recorded biological activity in humans for every species on the list; antioxidant, antibacterial, anti-inflammatory, antifungal/ antiprotozoal, antiviral, cytotoxicity/ antiproliferative, adipogenesis, MAA/ UV protection, matrix metalloproteinases, and blood fluidity were the main subjects. Most of the species on the list have been investigated for use, with only 3 unexamined, predominantly from species of small size that are difficult to identify without special equipment/ training. The major types of compounds responsible for observed activity were reviewed, with many being particular to one type of macroalgae. Intellectual property on the species was reviewed using Patentoscope, from the world intellectual property organization (WIPO). This revealed a wealth of patents that contained mentions of almost every species of algae in the study. Using patent classification schemes, the search was narrowed down to just 12 species that are the object of dedicated patents. *Undaria pinnatafida* and *Ulva lactuca* are the most commonly studied. Macroalgae can be considered a considerable source of relevant compounds for use in cosmeceuticals. Two species of invasive algae *Undaria pinnatafida* and *Sargassum muticum* were examined for their major compounds of interest, using different solvents. Extraction efficiency was solvent dependent, as well as resulting antioxidant activity. Glycerol was revealed to extract antioxidant compounds efficiently as compared to ethanol in *Sargassum muticum*.

Key words: Invasive seaweeds, cosmeticeuticals, bioactivity, intellectual property, *Sargassum muticum, Undaria pinnatafida*

Resumo

Com a globalização, o crescimento da população humana ao longo das costas e o clima em mudança, os ecossitemas costeiros estão sendo modificadas a uma taxa sem precedentes. Estas mudanças, têm originado a proliferação generalizada de macroalgas, com efeitos diversos nos ecossistemas afetados. No entanto, essa abundância também pode representar um manancial de oportunidades. A produção de cosméticos, e particularmente aqueles de origem natural, é alvo de grande procura. Muitas das espécies invasoras demonstraram atividade biológica que pode ser aplicada a produtos de cuidados da pele, os chamados "cosmecêuticos". Um levantamento de espécies "invasoras" comuns revelou 47 espécies, 16 Chlorophyta, 19 Rhodophyta e 12 Phaeophyta. Todos os seus efeitos estão interligados, mas o efeito mais comummente registrado foi a mudança de habitat, a mudança de processos nos ecossitemas e, finalmente, os efeitos genéticos. Os efeitos económicos são difíceis de quantificar, sendo a contenção e / ou a erradicação precoce os mais eficazes. Reutilizar algas de programas de contenção poderia ajudar a financiar essas operações, ou ser um incentivo adicional para a sua colheita. Realizou-se uma revisão da literatura de 198 artigos sobre a atividade biológica registrada em seres humanos para cada espécie analisada. Foram alvos deste estudo as atividades antioxidante, antibacteriana, anti-inflamatória, antifúngica, antiprotozoário, antiviral, citotóxico / antiproliferativo, atividade adipogénica, proteção MAA / UV, presença de metaloproteinases de matriz e efeitos na fluidez sanguínea. A maioria das espécies incluídas nesta lista foi estudada, sendo que apenas 3 não foram examinadas, predominantemente de espécies de tamanho pequeno que são difíceis de identificar sem equipamento ou treino especial. Foi feito um levantamento dos principais tipos de compostos responsáveis pela atividade observada, sendo muitos específicos de um tipo particular de macroalgas. A propriedade intelectual foi revista usando o Patentoscope, da organização mundial de propriedade intelectual (OMPI). Isso revelou uma riqueza de patentes que continham menções de quase todas as espécies de algas no estudo. Usando esquemas de classificação de patentes, a pesquisa foi reduzida a apenas 12 espécies, que são objeto de patentes específicas. A *Undaria pinnatafida* e *Ulva lactuca* são os mais comumente estudados, indicando que algumass macroalgas podem ser consideradas uma fonte considerável de compostos relevantes para uso como cosmecêuticos. Foram ainda realizados testes laboratoriais com duas espécies de algas invasoras *Undaria pinnatafida* e *Sargassum muticum,* as quais foram examinadas para os seus compostos de interesse, utilizando diferentes solventes. A eficiência de extracção foi dependente do solvente, assim como a actividade antioxidante resultante. O glicerol revelou maior eficiência de extração de compostos antioxidantes em comparação com etanol, em *Sargassum muticum*.

Palavras chave: Algas invasivas, cosmeticêuticos, bioatividade, propriedade intelectual, *Undaria pinnatafida, Sargassum muticum*

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Preface

The great blues seas, which cover our planet, have sustained humankind for centuries. Our slow mastering of their resources has been key to the evolution of societies and cultures as a whole. Today, new resources are becoming available with new tools and new perspectives. Traditional fisheries are under heavy pressure, but coastal communities can turn to new industries that do not put in danger the health of ecosystems.

Seaweeds are emblematic of life in the oceans. Despite some similarities to terrestrial plants, they are actually separate, highly complex and branched evolutionary lineages. In the West, societies have used them largely for technological purposes, starting with agricultural use of beach drift, and eventually production of iodine and jellifying sugars. In the East, they are highly integrated into traditional diets and medicine, and have been cultivated for centuries.

The cosmetics industry is a particularly appropriate venue for the use of macroalgae-derived extracts. Seaweeds are a well-known, but still deep well of bioactive metabolites, linked to the environmental conditions in which they thrive. Analogous to land plants, they are sessile and possess chemical-based defense systems from external stressors. They are routinely exposed to strong UV light, desiccation and biotic aggressions: all are important stressors of human skin.

Climate change and human exploitation of the oceans over the last century has created large perturbations of coastal ecosystems. The world's oceans are more and more interconnected through human activities, allowing species to colonize areas far from their initial ranges. Some of these are greatly advantaged by this change of habitat, massively proliferating in their new habitats. Blooms of native macroalgae are also being observed, due to omnipresent changes. These proliferations are often seen as nuisances, with conspicuous biomass accumulation and its associated effects. Putting effort into the revalorization of this cheap and abundant raw material can help to mitigate negative effects on the coastal ecosystem and diversify local economies.

The aim of this study was to identify potentially underexploited species of macroalgae, including relevant metabolites, for usage in the cosmetics industry. In this respect, a wide review of relevant literature was performed. The second goal was to investigate "green" extraction methods in order to extract the biomolecules of interest.

"Cosmetics do less than they say, but more than you think"

- Unknown

1. Literature review

Introduction

In the 21st century, humankind will be confronted with new challenges in the management of marine resources. Continued population growth, technological evolution, and changing consumer demands all have contributed, given rise to the need for more space, food, energy and trade, of which an increasingly larger share of goods and services comes from coastal and marine resources. The coastal environment is used for tourism, fishing, aquaculture, and energy production in close, even overlapping distribution (Douvere & Ehler 2009).

Green, brown and red seaweeds washing up and accumulating on shorelines is common in coastal regions across the globe. However, over the last few decades this phenomenon has been increasing (Smetacek & Zingone 2013). New species are growing in areas far outside their native distribution, to the alarm of inhabitants and surveyors alike. Assessing the real economic and ecological impact is necessary, important in the definition of actions to be taken. The impacts of introductions are nuanced and need to be evaluated on a case-by-case basis (Andreakis et al. 2012). Microalgal blooms have been identified as potential sources of valuable metabolites, however their harvest is the major technological hurdle (Kim et al. 2015); a constraint that does not necessarily apply to seaweeds (or macroalgae). Although these proliferations may be detrimental to local ecosystems or to coastal industries, they may also be opportunities following the harvest-for-use model.

Seaweeds are already the subject of a considerable industry worldwide, with value of cultured species production reaching US $5.6 billion in 2014, with the market somewhat concentrated in Asia (FAO 2016). The wide diversity of seaweeds provides an opportunity for the research and development of useful components (Rindi, Soler-vila, et al. 2012). They may be the source of mineral matter, polysaccharides, proteins, lipids, phytohormones, pigments and various other secondary metabolites (Bedoux et al. 2014), varying according to the overall genetic diversity and environmental conditions of their harvest (Mendes et al. 2013; Lann et al. 2012).

Modern skin care relies on a variety of active ingredients to better the appearance of the skin, which has given rise to a 121 billion dollar, and growing industry (Brandt et al. 2011, Trefis 2016). Seaweeds are already present in this industry in two ways, as an excipient in the formulation (i.e. stabilizer or emulsifier) - by far the most common scenario; or as the therapeutic agent itself (Morton DW 2013; Agatonovic-Kustrin & Morton 2013).

‘Cosmeceuticals’, as originally described by Dr. Albert Kligman for a hybrid category of products between drugs and cosmetics that exert a pharmaceutical therapeutic benefit but not necessarily a biological therapeutic benefit. Consumer demand in the West is mainly around natural products, such as plant extracts and in the East, seaweeds have been a part of culinary culture for hundreds of years. In this way, algae are an evident choice for research and development of cosmetic products.

Cosmeceuticals deal with a wide array of problems that are associated with the appearance of the skin. A healthy, youthful glow of the skin is a very valuable trait for the consumer, and many skin care formulas are designed with this effect in mind (Dayan 2008). Both types of aging increase the activity of matrix metalloproteinases that degrade structural proteins and polysaccharides, such as collagen and hyaluronic acid (Campisi 2005). As such, these activities are a priority when examining the effects and potential uses of seaweed extracts.

Day to day skin care implies maintaining proper hydration, protection against environmental stressors, as well as stimulation of the skins natural defenses. Seaweeds are exposed to stress similar to that human skin faces: desiccation; bacterial, fungal or viral infection; UV exposition; and exposure to reactive oxygen species. Moreover, seaweeds have been found to contain many compounds that may contribute to improved blood circulation (Kang et al. 2003), lipid metabolism (Ben Rebah et al. 2008; Kim et al. 2010) as well as anti-proliferative activities (das Chagas Faustino Alves et al. 2012). Many of the bioactivities listed below are linked and interact: i.e. antioxidants may play a role in reducing inflammation. For the sake of simplicity and brevity, bioactivities will be described as surveyed.

Antioxidants are widely included in cosmetics as both preservatives and active ingredients. The incorporation of antioxidant molecules is one the most popular ways to propose protection against pollution, UV light and other environmental stress. Free radicals are highly reactive molecules with unpaired electrons that can directly damage various cellular structural membranes, lipids, proteins, and DNA. The damaging effects of these reactive oxygen species is induced internally during normal metabolism and externally through various oxidative stresses. The production of free radicals increases with age, while the endogenous defense mechanisms that counter them decrease. This imbalance leads to the progressive damage of cellular structures, and thus, results in accelerated aging (Bogdan Allemann & Baumann 2008). Free radicals are also implicated in inflammatory processes, cancerous conditions, and various microbial infections. Whereas there is some debate on the long term beneficial effects of dietary antioxidants (Jerome-Morais et al. 2011) topical use is encouraged to reduce the harmful effects of UV radiation, maintaining skin well-being, and preventing dermal diseases (Pinnell 2003).

Similarly, seaweeds must protect themselves from bacterial, viral and fungal infection through the production of specialized phytochemicals. This can be very important in the ocean, with high prevalence of fouling organisms (Bazes et al. 2009; Rao et al. 2007). In this way, seaweeds may represent an important source for novel antimicrobial compounds, with particular interest for cosmetics. Avoiding contaminating microbial growth is important for ensuring shelf life, and ensuring good balance of the epidermal biota, for example in people suffering from acne.

Seaweed extracts can modulate cellular growth in a variety of ways. Most often, effects on cancer cellular lineages are investigated. Although out of the scope of cosmeceuticals, toxicity is an important part of inclusion of extracts, and toxicity can disqualify a particular extract/ compound for inclusion in common products. Influence on cellular metabolism, affecting processes such as lipidogenesis, and increasing microcirculation are several mechanisms proposed to reduce the appearance of cellulite for example (Rawlings 2006).

Metalloproteinases (EC 3.4.24) are ubiquitous endopeptidases containing a metal ion in their active site (Sárdy 2009). Part of the endogenous defense mechanisms, Matrix-Metalloproteinases (MMP) expression is modulated with UV exposure, intrinsic aging, wound healing and microbial infection. MMPs have been implicated in many physiological and pathological processes. These enzymes degrade structural proteins in the skin, i.e. collagen, inducing the appearance of fine wrinkles and a loss of elasticity over time. Expression of these enzymes can be increased intrinsically (Campisi 2005), or through external stress: several MMPs are inducted by UV radiation (Sárdy 2009), and they play an important role in acne pathogenesis (Papakonstantinou et al. 2005). MMPs play a pivotal role, along with their inhibitors, in regulating extracellular matrix degradation and deposition that is essential for wound re-epithelialization. Up-regulating several types of MMPs resulted in smaller scars on the same patent in sample studies (Caley et al. 2015). As such, these enzymes are very interesting targets for cosmeceutical screening.

Extremely important in skin aging and cancer generation, UV protection is a major sector in the cosmetics market. Many of the above ‘symptoms’: free radicals in the skin, MMP expression, mutagenesis can all be associated with exposure to the sun’s rays, not to mention painful sunburn. Seaweeds have developed several types of protection against UV rays, including the synthesis of screening and/or antioxidant molecules as well as enzymatic processes. The UV absorbing compounds in particular include some of the natural world's most potent UV blocking molecules at UVB (<300 nm) and UVA (> 300 nm) wavelengths (Mason et al. 1998). Seaweed extracts also affect cellular response to UV radiation through a variety of mechanisms including radical quenching, anti-inflammatory and antimutagenic effects (Schmidt et al. 2010; Guinea et al. 2012). Moreover, the safety of most common sunscreen products currently on the market is a contentious subject, whether it concerns metal nanoparticles or synthesized organic molecules (Krause et al. 2012; Hackenberg & Kleinsasser 2012; Franklin et al. 2007; Downs et al. 2016).

A common assay involving seaweed extracts is to examine their effect on serum. Many seaweeds will have serum coagulating, or fluidifying effects on human serum. Improving microcirculation is important in maintain a healthy look to skin. Skin whitening is especially popular in Asia, where lighter skin tones are preferred (E. P. H. Li et al. 2008). 'Detoxifying' and anti-pollution claims are growing in popularity around the world (Mintel Intelligence Group 2015).

With similar stressors to human skin, seaweeds could prove to be a valuable source of compounds for dermatological problems. Such 'active' ingredients will be the focus of the following review, with a focus on 'problem' seaweeds. In the interest of commercial use, ecological and environmental effects will also be evaluated, in order to establish the pertinence and reliability of each species as a source of raw material.

Invasive seaweeds and their impacts

In order to establish a list of invasive seaweeds to screen the first major step was a thorough review of the relevant scientific literature. The ecological characteristics of each species, growth type, introduction date/vector and ecosystem effects of each species were recorded from data included in the reviews Katsevanjekis (2014) and Davidson *et al.* (2015) when possible, and completed with a Google Scholar search and consultation of AlgaeBase Guiry & Guiry 2015 using the species name as a keyword.

For each index, a score of 0-5 was attributed to each species according to certain number of criteria. The score of a particular species source was related to the ease of obtaining biomass for that species (Table 1.1). Ease of obtaining biomass was arbitrarily linked to a) reports of biomass b) recurrence of reports c) reports of commercial exploitation.

Score	Description
1	Endangered/ Rare
2	Ephemeral blooms/ Non cultured
3	Cultured in trials/ Moderate seasonal standings
4	Limited cultivation/ some wild harvest
5	Cultivated at scale (EU) OR wild harvest with high production standards / Present in ingredient marketplaces

Table 1.1. Detail of SOURCE

The Google Scholar search engine was used, entering the keywords "invasive" + "macroalgae" AND/OR "seaweed". An initial list of invasive species was compiled from reviews on invasive species of algae, most notably S. Katvaneskis *et al.* (2014), concentrating on invasive species in general in European waters and Davidson *et al.* (2015), focalized on invasive species of macroalgae, this time with a more global view. From these sources, a list numbering 40 species (Table 1.2) was obtained. To not pass by native algae taking on "invasive" characteristics in their native habitats, the keywords "bloom" and "invasive" + "macroalgae" were also used on Google Scholar, which resulted in the addition of 8 species to the list.

Phylogenetic repartition

Among all of the different seaweeds screened (Table 1.2), Rhodophyta are the most prominent group of invasive species with 19 species screened. Next are the Chlorophyta with 16 species and finally Ochrophyta with the 12 remaining. Some genres are particularly well represented, such as *Caulerpa* and the bloom-forming *Ulva* both with five species, and well remarked for their invasive properties (Williams & Smith 2007). Others, such as *Sargassum* are also well represented with the recent blooms of *S. fluitans* and *S. horneri* in the Gulf of Mexico (Partlow & Martinez 2015), but also the very high profile *S. muticum* and more recent introduction of *Sargassum horneri* in California (Schaffelke et al. 2006; Stiger-Pouvreau & Thouzeau 2015).

Geographic repartition

Introductions of species outside of their native ranges is a commonly reoccurring scenario in today's ultra-connected world. The world's oceans are no exception. Increased shipping, intensifying aquacultural efforts, the rise of aquarium trade and Lessepian (Erythrean) migrations have spread multitudes of species to areas far outside their natural range.

The principal origin of invasive species of macroalgae by far, is the Western rim of the Pacific Ocean around the China Sea, with 17 species coming from this particular area. Indeed, the entire Indo-Pacific (excluding this area) accounts for 21 species, but englobes a much larger geographic area, ranging from the Red Sea to Australia. Europe, indeed the Atlantic in general, is relatively under-represented with only eight species described as invasive originating in Caribbean and European waters (Guiry & Guiry, 2016).

The most invaded marine areas as seen in this literature review are in Europe, and particularly the Mediterranean Sea (Table 1.2). In European waters alone, 986 alien species have been documented by DAISIE (2016) (Delivering Alien Invasive Species for Inventory in Europe). Worldwide, it is estimated that macroalgae represent 20% of successful marine introductions (Schaffelke et al. 2006). The Suez Canal is an extremely important vector for the introduction of alien species, accounting for 53% overall, all organisms included, but many other factors account for the vulnerability to invasive species (Coll et al. 2010). Following this geographic area, Hawaii is the next most invaded, with five species described as being invasive (Williams & Smith 2007; Davidson et al. 2015). Interestingly, the North-West Pacific has very few “invasive” species of algae described despite being a center of aquaculture and other intensive exploitation of oceanic resources Interestingly, although many species originate from the NW Pacific around the China Sea and to its North, the only invasive species recorded in the region is the aptly named *Ulva prolifera.* It was made famous by its massive proliferation before the Beijing Olympics of 2008. The “invasion” was in reality a bloom linked to a combination of factors involving aquaculture of this native algae and favorable oceanic water conditions, most notably high nutrient levels (Smetacek & Zingone 2013).

Order	Family	Species	Origin	Introduced/Invasive behavior	Source	Ecological effects
Charales	Characeae	*Chara connivens*	N Asia	Baltic Sea	1	HT
Bryopsidales	Caulerpaceae	*Caulerpa brachypus f. parvifolia*	Australia	Florida	2	SM
		Caulerpa cylindracea	S. Australia	Mediterranean	3,5	CC; SM; HC; TO; HT
		Caulerpa prolifera	Mediterranean	Florida	3	SM
		Caulerpa scalpelliformis	S. Australia	Brazil	2	SM; CC
		Caulerpa taxifolia	S. Australia	Mediterranean	5	CC; SM; HC; TO; HT
	Codiaceae	*Codium fragile fragile*	Japan	N. Atlantic; Med	5	SM; CC; HT; TO
		Codium isthmocladium	Caribbean	Caribbean	2	SM
		Codium parvulum	Red Sea	Israel/ Eastern Med	2	NI
	Dichotomosiphonaceae	*Avrainvillea amadelpha*	Circumtropical	Hawaii	2,5	CC; HC
Cladophorales	Cladophoraceae	*Chaetomorpha aerea*	Worldwide	-	3	SM
		Chaetomorpha linum	Worldwide	-	3	SM
Ulvales	Ulvaceae	*Ulva australis*	Australia/ Asia	N Spain	3	NI
		Ulva intestinalis	Baltic	-	3	TO
		Ulva lactuca	Brittany	-	5	TO
		Ulva prolifera	S. China Sea	-	3	CC; TO
Dictyotales	Dictyotaceae	*Stypopodium schimperi*	Red Sea	E. Mediterranean	2	SM; CC
Ectocarpales	Scytosiphonaceae	*Colpomenia peregrina*	N. Pacific	Europe	2	NI
Fucales	Fucaceae	*Fucus evanescens*	Circumpolar	SE Scandanavia	3	G
		Fucus serratus	Europe	NW Atlantic	5	SM; G
	Sargassaceae	*Sargassum fluitans*	Caribbean	-	3	TO
		Sargassum horneri	Japan/ Korea	California	5	CC
		Sargassum mangarevense	French polynesia	French polynesia	3,5	SM
		Sargassum muticum	Japan	NW Pacific; NE Atlantic	5	CC; SM; HT; HC
		Sargassum natans	Caribbean	-	3	TO

		Sargassum polycystis	Fiji/ SW Pacific Tuvalu	Tuvalu	3	HC
		Turbinaria ornata	French Polynesia	French Polynesia	3,5	SM
Laminales	Alariaceae	*Undaria pinnatifida*	NE Asia	SW/NE Atlantic, SW/NE Pacific, Med	5	SM; CC; HT
Bonnemaisoniales	Bonnemaisoniaceae	*Asparagopsis armata*	Western Australia	NE Atlantic; Med	5	CC; SM
		Asparagopsis taxiformis	Alexandria, Egypt*	Western Med	3	CC; SM
		Bonnemaisonia hamifera	W. Pacific	Scandanavia/N Europe	3,5	TO; HT; CC; SM
Ceramiales	Ceramiaceae	*Acrothamnion preissi*	Western Australia	Mediterranean	2	SM; CC; HC
	Dasyaceae	*Dasysiphonia japonica*	Japan/ Korea	NE/NW Atlantic	2	NI
	Rhodomelaceae	*Acanthophora spicifera*	Caribbean	Hawaii / Marshall Islands / Mexico	2	SM; CC
		Lophocladia lallemandii	Red Sea	Mediterranean	2,5	SM; CC; HT; TO
		Neosiphonia harveyi	Japan	NW Atlantic	2	NI
		Polysiphonia morrowii	NE Asia	Med; N Atlantic; SE Pacific	2	HT
		Womersleyella setacea	E Asia	Mediterranean	2	SM; CC; HT
Gigartinales	Caulacan-thaceae	*Caulacanthus ustulatus*	Europe	California/ Brittany	2	CC
	Cystocloniaceae	*Hypnea musciformis*	Circumtropical	Hawaii	5	SM; HC
	Soliericeae	*Kappaphycus alvarezii*	SE Asia	Hawaii/ Fiji/ India	5	SM
		Solieria chordalis	Europe	-	3,5	NI
Gracilariales	Gracilariaceae	*Gracilara salicornia*	S Asia	Hawaii	5	SM; CC
		Gracilara vermiculophylla	Japan	N Atlantic; East Pacific	5	CC; SM; HT; HC
Haly-meniales	Halymeniaceae	*Grateloupia turuturu*	Japan	N Atlantic; Australia	4	SM; CC; HT
Nemaliales	Galaxauraceae	*Galaxura rugosa*	Central-West Atlantic	Israel/ Med	2,5	NI

Table 1.2 Classification, origin and introduced range of species screened in this study. Green background: Charophyta and Chlorophyta; orange background: Ochrophyta; red background: Rhodophyta.SM : Space Monopolization ; CC : Community Change ; HC : Habitat Change ; HT : Higher Trophic levels ; TO : Toxicity ; G : Genetic effects. (Katsanevakis et al. 2014b; Davidson et al. 2015; Hoffman et al. 2014; Stiger-Pouvreau & Thouzeau 2015; Riosmena-Rodríguez et al. 2012; Reed et al. n.d.; Guiry & Guiry 2016)

Ranking by source

Potential availability of consistent quality biomass varied widely among the species listed. Although high recorded biomass was a positive factor for source ranking, it is near impossible to find estimations of biomass and general availability for many species. Several studies (Israel et al. 2010; Smith et al. 2004) speak of ephemeral blooms, but there is little follow-up and/or quantification of the biomass, repetitivity of such events. As such, these species received an inferior score to species relatively well studied and easily available via European seaweed resellers. Generally, ease of sourcing is directly linked to the other factors in consideration, such as alimentary and phycocolloid production by said species. If there is no information on the properties of a particular seaweed there cannot be demand for it.

Of note are the species that are currently commercially exploited in Europe or Asia: several species on the list have been trialed even in areas outside of their native range such as *Gracilaria vermiculophylla, Codium fragile* and *Ulva* sp (Abreu et al. 2011; Silva & Abreu 2014). The highest scores were attributed to the most readily available species, with extracts on the cosmetic ingredient market and often mass cultivated in Asia and the Indo-Pacific such as *Undaria pinnatfida, Kappaphycus alvarezii* and *Hypnea musciformis.* The lowest score attributed was to the unique Charophyte, *Chara connivens*, found in the Baltic and introduced by ballast sand in the 19th century. The species is relatively rare and now subject to active protection efforts (Kotta et al. 2004), and as such it is strange that it made Andreakis's list of invasive species.

Ecological and Economic Consequences

Assessing the impact of invasive species of seaweeds is a challenging endeavor. First and foremost, the lack of knowledge and robust data hinders objective judgment. Globally, only 10% of non-indigenous species have been subject to ecological impact studies (Davidson et al. 2015): the most often in areas close to research centers and touristic zones. Economic impacts are rarely published. Ecological impact studies, when performed, are often of limited scope and prone to error (Davidson & Hewitt 2014). Even basic identification of seaweeds can be difficult for non-experts (Rindi, Soler-vila, et al. 2012), due to the morphological plasticity that occurs within, as well as similarities between seaweeds. As such cryptic invasions may occur where non-native replace native morphologically similar species (Tano et al. 2015). Information in this domain is still too sparse to identify general patterns and mechanisms of impact. This is a critical knowledge gap as rates of introductions and hence impacts of nonindigenous macroalgae are expected to accelerate with climate change and increasing global trade connectivity.

Three common hypotheses exist for the action of invasive species on their adopted ecosystems, using the analogy of a car, the driver, passenger (MacDougall & Turkington 2005) and back seat driver models (Bauer 2012). In the driver model, the invasive species is at the origin of the disturbance/ ecosystem change. Concerning the passenger model of invasion, the invasive species is more of a symptom of ecosystem change rather than a direct cause of it. Finally, the back seat driver invasive species requires or benefits from disruptions of ecosystem, but also add to changes in ecosystem properties and further the decline of native species. With environmental perturbations, such as climate change, nutrient enrichment, or excessive exploitation of a keystone species, other native species may proliferate to the extent that can be considered invasive.

Even if not entirely predictable, some factors of both the species and the ecosystem of introduction highly contribute to the success and extent of an invasion. Notably, successful marine introductions are dependent on the presence of a transport vector, uptake of propagules and journey survival of the species. The similarity in environmental conditions between the original and receiving habitats is key to the establishment of non-indigenous species. Some biological traits of the invader to facilitate establishment (Schaffelke et al. 2006). Some biological traits are prevalent in invasive species of seaweeds: high growth rates and large individual sizes; vegetative propagation; high levels of sexual reproduction and high fecundity; parthenogenetic reproduction and broad environmental tolerances (Andreakis et al. 2012). Overfished, polluted, or otherwise stressed and unstable ecosystems are also more vulnerable, as well as evolutionarily isolated areas. (Vaz-Pinto et al. 2014; Schaffelke & Hewitt 2008). Nonetheless, several reviews have attempted to quantify/ qualify the ecological impacts, for example Schaffelke et al. 2006; Williams & Smith 2007; and Katsanevakis et al. 2014b. These studies performed meta-analysis of the data presented in various research papers from across the globe in terms of ecological and evolutionary impacts, invasive seaweeds may affect their novel biotopes in several manners.

Firstly, through direct and indirect competition with native biota, for light or substratum for example. This can be manifest through space monopolization (SM), in this case, the species physically occupies space where native species grew beforehand, and effectively “blocks out” their growth. This goes hand in hand with change in community composition. This reflects modified biodiversity of the novel habitat, notably in terms of population sizes. Effects on higher trophic (HT) levels, being the presence of herbivores and repercussions through trophic webs.

• Habitat change (e.g. changed structure, sediment accumulation)

• Change of ecosystem processes (e.g., alteration of trophic structure).

• Genetic effects:

- Introgression: within a species
- Hybridization: between species

The recorded ecological effects of the species screened in this study are presented briefly in Table 2. The most common ecological effect recorded is SM, which is a characteristic of 27 of the species. This effect if often concurrent with community change (CC), investigated for 21 of the species. The next level investigated is the influence on higher trophic levels (HT), investigated for 12 species. Toxicity (TO) is recorded for 10 species (mainly due to the effect of decomposition of abundant algal mass, but also the production of allopathic chemicals for example). Habitat change (HC) reflecting a physical change in the habitat, through the accumulation of sediments for example is noted in eight species. For two species, genetic (G) effects are recorded, where the invasive species (here the *Fucus* species) hybridized with local species. It is important to note that even though a species does not have a recorded influence for a given effect, this can be just be an observational oversight. Seaweeds affected macroalgae were the taxonomic groups with the second highest average numbers of impacted ecosystem services as reported by Katsanevakis et al (2014). Furthermore, *Sargassum muticum* was one of the three introduced species (all taxonomic levels compounded) affecting the highest number of ecosystem services (10) in that review concerning the effects of invasive species in Europe's marine environments.

Economic and societal impacts are both direct and indirect. Direct impacts include costs of loss of ecosystem functions or values, impacts on environmental amenity, and impacts on human health. Indirect impacts are management costs (government/non-government), costs of research into introduced species, and costs for eradication and control measures.

Table 1.3 presents costs and/or human effort estimates of the removal of some invasive seaweeds. It is important to note that these costs are incomplete; an economic assessment of the impacts of seaweed invasions should cover all potentially affected values including use and non-use values. As much as possible, estimates should include other societal costs such as management and research. However, it is impossible to identify the proportion of these expenses that apply to seaweed invasions only (Schaffelke & Hewitt 2008). Evidently, the costs of containing and complete eradication are very high.

However, on the flipside, some metabolites of these seaweeds are extremely valuable. For example, on current marketplaces Fucoxanthin retails at around 70 000 euros/kg when sold as a nutritional supplement (as a rough extrapolation from products available on Amazon® marketplace). With content reaching 7 mg/g DW of *Undaria pinnatifida*, cosmetics containing fucoxanthin rich extracts create high added value products from “waste”. If containment and not eradication is the goal, this can be a benefit. Because of environmental fluctuations, controlling development in restrained areas is probably the most cost effective and easiest to way to get the seaweed biomass to market: environmental condition can be monitored and quality of raw material justified.

Species	**Summary**	**Cost/ Effort**
A. spicifera	Experiments with multiple methods (manual removal, shade, biological control) to reduce and/or remove from Kaloko Fishpond, Hawaii	1–3 pers cont. of 4.5 ha pond
A. amadelphia	Removed from 9 ha of reefs, Waikiki Hawaii	Indirect: USD$20,994
C. fragile	Mortality of cultured oysters; loss of ecosystem functions or values via displaced kelp; Prince Edward Island, Canada	CAD$1,5M $year^{-1}$; projected up to CAD$32M
C. taxifolia	Rapid response, containment and ongoing monitoring of incursion in California, USA (2000–2005)	7.6M USD
	New South Wales Australia, application of Sea Salt Total estimated cost to treat all affected areas in state ($8km^2$)	5-23 USD/m^2 46M USD
	Freshwater treatment, South Australia	4M USD over 4 years
	Decreased yields for artisanal fisherman, increase in some costs (fuel, maintenance of gears and opportunity costs)	NA
H. musciformis	Removal of biomass from beaches in Kihei, Maui, Hawaii	55000/ year
K. alvarezii	Removal from coral reefs in Hawaii	~2 pers/ hr/ m^2
N. harveyi	Pest on carageenophyes; Philippines	7-69% yield reduction
S. muticum	Manual removal by volunteers (group size unknown)- England	10-70 kg/ trip
	Estimated cost for mechanical removal (experimental) - England	~38$/ t
U. pinnafidata	Removal from sunken vessel in Catham Islands, New Zealand (Heat treatment/ monitoring)	USD>1.9 M
	Manual removal (experimental scale)	23000 USD/year
	Monitoring and removal *Undaria pinnatifida* from Monterey Harbor, California over a 10-year period	US$160,300

Table 1.3. Economic costs associated with eradication and control efforts for invasive seaweeds. Where no monetary value was available, an estimate of effort is given. Adopted from Schaffelke & Hewitt 2008 and Davidson et al. 2015 and references therein

In terms of perceived impact, there is a definite perception bias against non-native species in both popular and scientific press. In the former for example, *Caulerpa racemosa* was known as “Algue tueuse (Killer Weed)” (Barelli 2011), and *Sargassum horneri* is called “Devil Weed” in its newly colonized habitat off California (Orlowski 2015). The original “Killer Weed” is now receding in many invaded areas, and the “Devil Weed” is not yet the subject of serious scientific publications (at time of writing 2016). This question is subject to debate; it is important to recognize potential positive effects of introduced species (see review by Andreakis et al. 2012). Alien species may in fact benefit certain components of native biodiversity and can enhance existing and/or provide new ecosystem services (Katsanevakis et al. 2014a). However, in relatively well observed ecosystems in the US and Australia, researchers tend to err on the side of caution: unknown/under evaluated impacts are considered by default to be negative (Davidson & Hewitt 2014).

Another perception bias might be cultural: the NW Pacific, that is to say China, Japan and Korea have almost no “invasive” species. Only *Ulva lactuca* is present, and this is because of its bloom forming behavior. Have introductions simply followed the flow of knowledge of aquacultural and seaweed rearing techniques, or do researchers in these areas disregard the presence of new species in their areas if they are directly interrupting some kind of economic activity?

Introduced invasive species can also be a source of “inspiration” for research on local species. Seaweed genera often contain many representatives, which may in turn show promising, related metabolites to those present in non-native species. This can help in their protection and/or the development of new resources with the advantage of control of intellectual property and exclusivity in production. In fact, this was listed as a ‘positive effect’ in Katsanevakis et al.’s (2014) review of the impacts of non-indigenous species in European coastal marine ecosystems.

Bioactivity and Intellectual Property

To determine the research effort on individual species the following methodology was used. A list of commonly investigated bioactivities was compiled and each species found in Table 1.2 list screened in the following manner “sp name+ bioactivity”, where bioactivity was any of the following 10: Antibacterial; Blood fluidity; Anti-inflammatory; Antifungal/protozoal; Antioxidant; Antiviral; Cytotoxicity/ Antiproliferative effects; Lipid Metabolism; UV exposition/photoprotection; Matrix-Metalloproteinase Inhibition (see Table 1.4). The names of the specific enzymes: elastase, lipase, etc were also used to avoid omission of any relevant articles. The nature of the extract was recorded along with a brief description of results, for example: aqueous extract, slight activity Kamehaha 1987 is presented in Supplement. Texturing agents (phycolloids) were not included in this study, although they are extensively used in cosmetics.

Data concerning the intellectual property rights on each species was examined to determine its importance from a commercial/ industrial standpoint (Table 6). For this, the World Intellectual Property Organization (WIPO) database https://patentscope.wipo.int/search/en/search.jsf was consulted with the query "species name" for each species in the list in the field "FULL TEXT". This revealed a total of 3744 patents containing the names of the species in the list.

Next, the number of patents filed under the most relevant domain for cosmetics was recorded. The International Patent Classification (IPC) provides a classification for patents for invention including published patent applications, inventors' certificates, utility models and utility certificates. The Classification, being a means for obtaining an internationally uniform classification of patent documents, has as its primary purpose the establishment of an effective search tool for the retrieval of patent documents by intellectual property offices and other users, in order to establish the novelty and evaluate the inventive step or non-obviousness (including the assessment of technical advance and useful results or utility) of technical disclosures in patent applications. Each patent is filed under a hierarchal scheme (Figure 1.1).

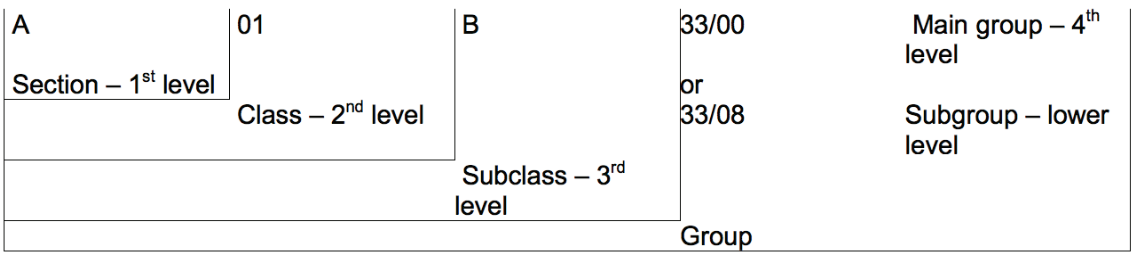

Figure 1.1. International Patent Classification scheme (Wipo 2016)

The Classification represents the whole body of knowledge which may be regarded as proper to the field of patents for invention, divided into eight sections. Sections are the highest level of hierarchy of the Classification. Each section is designated by one of the capital letters A through H. The section title is to be considered as a very broad indication of the contents of the section. The eight sections are entitled as follows:

A HUMAN NECESSITIES
B PERFORMING OPERATIONS; TRANSPORTING
C CHEMISTRY; METALLURGY
D TEXTILES; PAPER
E FIXED CONSTRUCTIONS
F MECHANICAL ENGINEERING; LIGHTING; HEATING; WEAPONS; BLASTING
G PHYSICS
H ELECTRICITY

Within sections, informative headings may form subsections, which are titles without classification symbols. For example, the Section A (Human Necessities) contains the following subsections: Agriculture Foodstuffs; Tobacco Personal or Domestic Articles Health; Life Savings; Amusement.

Next, each section is subdivided into classes, which are the second hierarchical level of the Classification (see Figure 1.1). Cass symbol consists of the section symbol followed by a two-digit number, which references the category. Each class comprises one or more subclasses which are the third hierarchical level of the Classification. Finally, subclasses are themselves broken down into “groups”, which are either called main groups (i.e. the fourth hierarchical level of the Classification) or subgroups (i.e. lower hierarchical levels dependent upon the main group level of the Classification) (Wipo 2016).

Following the above logic, seaweed extracts considered relevant to this study would be filed under the IPC code A61K. Following the above logic, this designates:

Section A: Human Necessities

Class 61: Medical and Veterinary Science, Hygiene

Group K: Preparations for Medical, Dental, or Toilet Purposes

Subgroup 7/00: Cosmetics or similar toilet preparations

The data returned by the query for each species name (ex: “Asparagopsis armata’) was examined using built-in analysis of the database, and the number of patents filed under the code A61K relating to cosmetic formulations was recorded for each species.

To refine the above search, the database was searched a second time: limiting results to patents containing the species name on the front page of the patent, and under the identifier A61Q. A61Q covers ‘specific use of cosmetics or preparations thereof’, and would be covered in A61K, but it is much more restrained in its scope. This considerably narrowed the field of patents. Although the results were not considered for the above analysis, the patents were individually read to gain insight on the usage of each species.

Finally, the industry platform “UL Prospector” was reviewed in order to see the direct commercial offer of the seaweeds as “active ingredients”. Species present on the market were recorded, as were the companies producing extracts, the International Nomenclature for Cosmetic Ingredients (INCI) and claims behind each extract were recorded.

Bioactivity

The initial screening of literature related to the bioactivities of each species resulted in 198 articles. Table 1.4. shows the results of the initial screen, a more complete version is available in annex (including details about type of extracts and effects). When a certain bioactivity was not investigated, NI for "Non-investigated" is listed as the result. If several publications refer to the same type of bioactivity, they are included in the results. In this way, the screen is relatively exhaustive of the types of bioactivity investigated for each species.

From an experimental standpoint, "crude" extracts using organic or aqueous solvents are the most common way of screening for bioactivity in seaweeds. This strategy is useful for broad screens of algae extracts to detect any substantial and easy to observe biological activities quickly. If an interesting effect is observed, the nature of the solvent will point in the direction of the metabolite responsible. However, the complexity of these mixes may confound results if there are antagonistic effects in the broad spectrum of molecules extracted by these methods. As such, initial crude extracts need to be fractionated/ purified to identify the exact molecular agents at play for an observed activity.

The prevalence of certain species and geographic areas became apparent as well in the literature review. Interestingly, many of the articles found here concerning the bioactivity of seaweed extracts came from regions around the seaweeds origin. Although the majority of the invasive species listed here belong to the Rhodophyta, they are not necessarily the group that has the deepest ecological impact. In fact, the species with the highest profile relatively speaking are *S muticum, U pinnatifida* and *Ulva lactuca*, brown and green algae respectively (Katsanevakis et al. 2014a; Davidson et al. 2015). Unsurprisingly these "high-profile" invaders have received a large focus of scientific effort concerning their respective bioactivities. Three species, *Womersleyella seteceae, Codium parvulum*, and *Neosiphonia harveyi* have not yet been investigated for any potential bioactivities.

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Species	Antioxidant	Antibacterial	Anti-inflammatory	Antifungal/ Antiprotozoal	Antiviral	Cytotoxicity/ antiproliferative	Adipogenesis	MAA/UV protection	MMP	Blood fluidity
C. connivens	NI	+	NI	-	NI	NI	NI	NI	NI	NI
A. amadelpha	NI	+	NI	NI	NI	NI	NI	NI	NI	NI
C. parvifolia	NI	NI	NI	NI	+	NI	NI	NI	NI	0
C. prolifera	+	+++	+	+	+	+	+	NI	NI	0
C. racemosa	+	+++	+	+	+	+	+	+	NI	0
C.scalpelliformis	+	+	+	+	+	-	NI	NI	NI	NI
C. taxifolia	+	++	NI	+	+	+	+	NI	NI	NI
C. aerea	+	+	NI	-	-	NI	NI	NI	NI	+
C. linum	+	+	-	NI	-	+	NI	-	NI	0
C. fragile fragile	+	+	+	+	+	+	+	+	NI	+
C isthmocladum	-	+	+	-	NI	+	NI	NI	NI	+
C. parvulum	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
U. australis	NI	+*	NI	+*	NI	NI	NI	NI	+	NI
U. intestinalis	+	++	NI	+	-	+	+	-	NI	+
U. lactuca	+	++	++	+	++	++	+	-	+	+
U. prolifera	NI	+	NI	NI	NI	NI	NI	NI	NI	NI
C. peregrina	NI	+*	NI	-	-	-	NI	NI	NI	NI
F. evanescens	++	++	NI	NI	+	+	+	+	-	NI
F. serratus	+	++*	+	NI	NI	+	NI	NI	NI	+
S. fluitans	+	+	NI	+	NI	-	NI	NI	NI	NI
S. horneri	++	+	+	NI	+	+	+	+	+	+
S. mangarevense	++	+	+	-	NI	NI	NI	NI	NI	NI
S. muticum	++	+*	+	+	+	+	NI	+	NI	NI
S. natans	NI	+	NI	+	NI	NI	NI	NI	NI	NI
S. polycystum	+	+++	+	NI	NI	+	+	NI	NI	NI
S. schimperi	NI	NI	NI	NI	NI	+	NI	NI	NI	NI
T. ornata	+	++*	+	+	-	+	+	NI	NI	+
U. pinnatifida	+	+	+	-	+	+	+	+	+	+

*Table 1.4. Bioactivity of selected species of seaweeds. +: extracts present selected bioactivity. - : Extracts do not present selected bioactivity *conflicting reports/ indirect activity. In 'Antibacterial' column: '-' no antibacterial effect; '+' slight effect (1 strain); '++' moderate effect (2-3 strains); '+++' broad spectrum effect. In Anticoagulant column: '-' hemagluitinaing effect; 0 no effect on blood; '+' anticoagulant. Antioxidants: '+' moderate activity; '++' strong activity.*

Species	Antioxidant	Antibacterial	Anti-inflammatory	Antifungal/ Antiprotozoal	Antiviral	Cytotoxicity/ antiproliferative	Adipogenesis	MAA/ UV protection	MMP	Blood fluidity
A. spicifera	+	+	+	+	NI	+	NI	+	NI	-
A. preissi	NI	-	NI	NI	NI	NI	NI	NI	NI	NI
A. armata	+	+++	NI	+	+	+	NI	+	+	-
A. taxiformis	+	++	NI	+	NI	NI	NI	+	NI	+
B. hamifera	+	+++	-	+	NI	+	NI	+	NI	NI
C. ustulatus		+	-	+	NI	+	NI	NI	-	NI
D. japonica	NI	NI	NI	NI	NI	-	NI	NI	NI	NI
G. rugosa	-	+	+	+	+	-	NI	NI	NI	NI
G. salicornia	+	++	NI	+	+	+	NI	NI	NI	-
G. vermiculophylla		+	NI	+	NI	NI	+	+	NI	NI
G. turuturu		++	-	+	+	-	NI	+	NI	NI
H. musciformis	+	++*	+	+	+	+	NI	NI	+	-
K. alvarezii	+	++*	-	+	+	-	NI	NI	-	-
L. lallemandii	NI	-	NI	NI	+	+	NI	NI	NI	NI
N. harveyi	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
P. morrowii	+	+	NI	NI	+	NI	+	+	NI	NI
S. chordalis	NI	NI	+	NI	+	-	NI	+	NI	-
W. setacea	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

*Table 1.4 (Cont.) Bioactivity of selected species of seaweeds. +: extracts present selected bioactivity. - : Extracts do not present selected bioactivity *conflicting reports/ indirect activity. In 'Antibacterial' column: '-' no antibacterial effect; '+' slight effect (1 strain); '++' moderate effect (2-3 strains); '+++' broad spectrum effect. In Anticoagulant column: '-' hemagglutinating effect; 0 no effect on blood; '+' anticoagulant. Antioxidants: '+' moderate activity; '++' strong activity.*

Antibacterial activity was the most commonly investigated type of biological activity. Only seven species have not been explored for antibacterial activity out of the 48 surveyed here. Anti-Inflammatory activity, antioxidant, and cancer cell cytotoxicity have all been subject to at least a cursory examination in 33 species each. Anti-viral and anti-inflammatory activity along with action on blood coagulation were examined in 25, 24 and 23 of the species respectively, or approximately half of the pool of species. Least examined were effects on UV protection, adipogenesis, and Matrix-Metalloproteinases (notably collagenase, elastase and hyaluronidase) with 19, 15 and 10 species extracts being investigated for these specific activities.

Antibacterial assays may be the easiest and cheapest type of assay to perform with limited amounts of material. How research is oriented, with drug or medical type applications being generally higher priorities than cosmetic applications is well reflected here. Medical applications justify more precise, and costly, extractions of metabolites that were identified as responsible for a particular bioactivity.

Metabolites of interest

Seaweeds are a rich resource of bioactive molecules, with many being exclusive to the respective kingdoms of green, red and brown seaweeds. To mention but a few of the many types of molecules synthetized by algae there are polysaccharides, carotenoids, polyphenols, mycosporine like amino acids, proteins and peptides, and many, many more. Table 1.5 shows examples of metabolites found in the invasive species that were screened here.

Family/ genus	Biologically Active Metabolites
Bonnemaisoniales	• Sulfated Polysaccharides (Haslin et al. 2001) • MAAs (Figueroa et al. 2008; Karsten et al. 1998); • Halogenated compounds (Dembitsky & Srebnik 2002; Greff et al. 2014)
Caulerpa	• Sulfated Polysaccharides (Lee, Hayashi, Maeda, et al. 2004) • Lectins (Cavas & Pohnert 2010) • Glycolipids (Wang et al. 2007) • Sesquiterpenoids : Caulerpenyne ; caulerpals (Cavas et al. 2006) • Pigments : Caulerpin (de Souza et al. 2009)
Codium	• Sulfated Polysaccharides (Ciancia et al. 2007) • Clerosterol (A. D. Kim et al. 2013) • Carotenoids : Siphonaxanthin (Ganesan et al. 2010)
Gracilaria	• Phycobiliproteins : R-phycoerythrin (de Almeida et al. 2011) • Prostaglandins (Kanamoto et al. 2011) • Carotenoids : violaxanthin/ antheraxanthin (Schubert et al. 2006) • MAA (Roleda et al. 2012)
Fucus	• Glycolipids (Imbs et al. 2009) • Polysaccharides : Fucoidan, fucans (Lapshina et al. 2006) • Carotenoids : Fucoxanthin (Imbs et al. 2013)

	● Phlorotannins (Imbs et al. 2009)
Ceramiales	● Alkaloids (Gross et al. 2006) ● Carotenoids : Lutein group (Schubert et al. 2006)
Sargassum	● Polysaccharides : Fucoidan, fucans (Shao et al. 2014) ● Sargachromenol (J. A. Kim et al. 2012) ● Carotenoids (Lann et al. 2012)
Ulva	● Sulfated Polysaccharides : Ulvans (Lahaye & Robic 2007)

Table 1.5. Some examples of bioactive metabolites present in the seaweeds screened

Polysaccharides

Seaweeds are rich sources of polysaccharides (PS) including some that have become well-known (and valuable) additives in the cosmetics industry for their rheological modifying gelling and thickening properties. Each major type of seaweed, red brown or green has characteristic types of polysaccharides, indeed their abundance and variety deserves special attention, out of the scope of this review.

PS are polymeric carbohydrate chains of monosaccharides (galactose, glucose, mannose, fucose, galactans, xylose, etc.) bound together by glycosidic linkages. Their properties depend on a wide variety of factors including molecular weight, chemical composition and chain conformation (de Jesus Raposo et al. 2015; Pomin 2012; Ngo & Kim 2013). Many, if not most, seaweed PS contain sulfate moieties, whose position and number contributes greatly to their structural or biological activities (Patel 2012).

Galactans are found most notably in red algae: the agarans and carrageenan. These sulfated galactans are the subject of a huge international industry. *Hypnea musciformis* is an extremely abundant alga that is commercially cultivated for its kappa carrageenan. Besides rheology modifying properties, SGs from this seaweed reduce NO pathway dependent neutrophil migration and subsequent inflammatory response (De Brito et al. 2013). SGs from the same species show strong antioxidant activity under lipid peroxidation assay and through hydroxyl radicals scavenging (das Chagas Faustino Alves et al. 2012). However, sulfated galactans are not restricted to red algae. Indeed, extracts of galactans from *Caulerpa* genus species also showed good antiviral effects, notably Herpes Simplex Virus, a common pathogen transmissible by touch (Lee, Hayashi, Maeda, et al. 2004; Ohta et al. 2009). Moreover, polygalactosides react with the protective outer surface of the skin and the ion–ion interaction form a protective moisturizing complex (Ngo & Kim 2013).

Fucans are sulfated polysaccharides that are composed of a fucose backbone, and characteristic of brown algae. Fucoidan (Figure 1.2) could be considered the ‘star’ in this category considering the wealth of data on its biological properties. Cumashi et al. (2007) isolated fucoidan fractions from 9 brown seaweeds (including *Fucus spiralis* surveyed here) and showed that all had its anti-inflammatory effect through inhibition of leucocyte recruitment. It has been the subject of extensive study, shown have anti-allergenic potential (Maruyama et al. 2005), antioxidant effects (Kang et al. 2008) inhibit several MMPs (Ku et al. 2010) and more (see review by Li et al. 2008). Furthermore, fucose polymers are hygroscopic and act as hydrating agents (Wijesinghe & Jeon 2011).

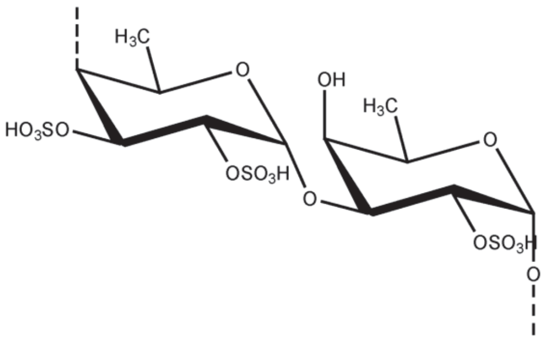

Figure 1.2. Fucoidan (Thomas et al. 2014)

Green algal polysaccharides, the ulvans are the least characterized of the major seaweed polysaccharides (Lahaye & Robic 2007), although they are good moisturizing agents, resembling hyaluronic acid (Surget et al. 2016); antioxidants; immunostimulants; as well as stimulators of collagen production and cell proliferation (Alves et al. 2013). Some are also dose-dependent, strain-specific and selective antivirals: Arabinose-xylose-rhamnose-galactose-mannose-glucose in ratio 1:1:9:5:2.5:16 from *U. lactuca* is one such example (Ivanova et al. 1994).

Extraction methods focalized on PS mostly rely on heated water to hydrolyze bonds and disrupt cross-linking to solubilize material. Several step processes, like those used for the extraction of rheological modifiers can be used for bioactive metabolites. In mild acid extraction, for example phenolic compounds and pigments are extracted with organic solvents in an initial step, before acidic processing. PS can be precipitated from solution by the addition of Calcium or other ions. Ultrafiltration techniques using molecular weight cut-offs are relatively economical for obtaining higher-purity PS of specific molecular weights. Balboa et al (Balboa, Rivas, et al. 2013) achieved good yields of fucoidan with hot water extraction of *S. muticum,* although with moderate TEAC antioxidant activity, equivalent to about 0.25 g Trolox.

Carotenoids

Nature's most widespread pigments, carotenoids are linear polyenes that function both as light energy harvesters and as antioxidants that inactivate reactive oxygen species formed by exposure to UV light and air. Seaweeds are especially rich in these pigments, with many being distinct to certain classes and families (Takaichi 2011). Carotenoids are linear polyenes that can be classed into into carotenes, which are unsaturated hydrocarbons, and xanthophylls, which present one or more functional groups containing oxygen (Cuellar-Bermudez et al. 2015).

Fucoxanthin, found in brown algae, has been the subject of many studies and subsequent reviews (see Peng et al. 2011) which include: antioxidant, anti-inflammatory, and cancer cell cytoxicity. For example, among 30 species of seaweeds found in Hawaiian waters, *Turbinara ornata* showed the highest antioxidant capacity (FRAP assay). The authors determined via fractionation and HPLC that the compound responsible for the activity was indeed fucoxanthin (Kelman et al. 2012). The molecule also shows photoprotective effects that are unrelated to its antioxidant activity: such as the promotion of skin barrier formation through induction of fillagrin (Matsui et al. 2016).

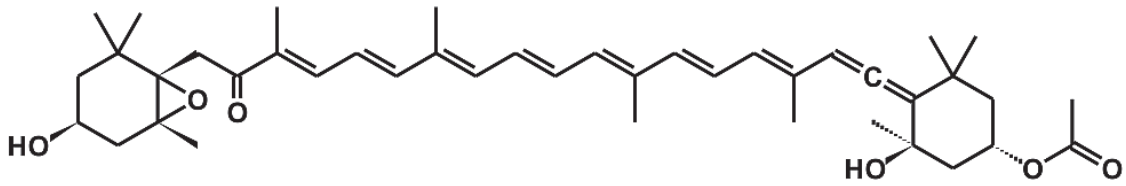

Figure 1.3. Fucoxanthin

Other carotenoids, such as lutein and zeaxanthin have antioxidant activity and may play a role in direct absorption of near UV light (Schubert et al. 2006). They can be found in all of the red seaweeds screened in this review. Siphonaxanthin is another very interesting carotenoid with similar anti-cancer, antiangiogenic and anti-inflammatory effects (Sugawara et al. 2014). It is notably produced by the Codium species screened here (Ganesan et al. 2010).

Carotenoids are often found in crude organic extracts, as they are readily soluble in this type of low or non-polar solvent. Much of the the xanthophyll type carotenoids in seaweed cells are esterified. Thus, the extraction can be facilitated by using a slightly acidic medium (Milledge et al. 2015).

Mycosporine-like Amino Acids

Mycosporine-like amino acids (MAAs) are a group of particularly interesting molecules for research purposes. MAAs are colorless, and water-soluble compounds with a cyclohexenone chromophore conjugated to a nitrogen substituent of either an amino acid or imino alcohol. They are the naturally occurring molecules that absorb the strongest in UV wavelengths (Schmid et al 2003) and have long been considered for use in sunscreens (Mason et al. 1998). In macroalgae, expression levels are quickly enhanced upon exposure to high photosynthetically active radiation and UV. Further evidence of the UV shielding role of these compounds is the accumulation of these molecules in the eyes and other sensitive organs of reef fish and invertebrates that are unable to synthesize this type of molecule (Shick & Dunlap 2002).

Furthermore, they also have synergistic properties for sunscreens going beyond that of UV absorption. Their antioxidant potential (Wada et al. 2015), slight inhibitors of collagenase (Hartmann et al. 2015), promote cell growth (Oyamada et al. 2008) and wound healing (Choi et al. 2015). In trials where they were included in sunscreen, application of MAAs on the skin of women between the ages of 36 and 54 resulted in improvements in skin firmness, smoothness and wrinkle depth (Wada et al. 2015). These effects have been shown for several MAAs, namely Shinorine and Porphyra 334, but there are over 30 MAAs (Sinha & Sinha 2013). As such, these molecules are exciting candidates for further research and development.

Presence of MAA is predominant among rhodophytes in macroalgae. Eight species of red algae screened here contained MAAs, although quantities were not systematically examined (see Table 1.6). Although some authors have detected small quantities in species such as Ulva – this may be due to epiphytic contamination.

Species	MAAs	Quantity (mg/g DW)
Acanthophora spicifera	Mycosporine-Glycine	0.014 ± 0.001
	Porphyra 334	1.960 ± 0.151
	Palythine	0.112 ± 0.026
	Asterina-330	0.029 ± 0.007
	Palythinol	0.033 ± 0.001
	Palythene	0.004 ± 0.001
Asparagopsis armata	Shinorine	~ 2
	Palythine	~ 0.5
	Asterine 330	Traces*

Asparagopsis taxiformis	Palythine Shinorine	0.005 ± 0.002 0.005 ± 0.001
Bonnemaisonia hamifera	Putative (Piao et al 2012)	Non investigated
Gracilaria vermiculophylla	7 types detected non identified (Roleda et al 2012)	Not quantified
Grateloupia turuturu	Shinorine Palythine	~ 2.7 ~ 0.3*
Hypnea musciformis	Putative (Schmidt et al 2012)	Not investigated
Solieria chordalis	Palythenic acid	Not quantified

*Table 1.6. Presence and quantities of MAAs in Red Seaweed; *Values derived from maximum MAA content and mean MAA proportions as communicated by authors (Karsten et al 1998, Figueroa et al. 2008; Groniger et al 2000)*

MAAs are sold for use in cosmetics, although in dilute aqueous solutions for example HelioNori by the French company GELYMAR, as well as the older and more well known Helioguard 365 (Mibelle Chemistry Switzerland), which sells a *Porphyra* extract in liposomes.

The chemical nature of MAAs make their extraction relatively straightforward, even if concentration becomes a problem at scale. The highly polar nature of these compounds encourages the use of slightly acidic aqueous solutions, or cold methanol or ethanol solutions to obtain MAA-rich fractions (La Barre et al. 2014; Volkmann & Gorbushina 2006).

Phenols

Phenolic or polyphenolic compounds are also products of the secondary metabolism of algae and comprise a large and diverse group of chemical compounds, consisting of a hydroxyl group (–OH) directly bonded to a benzene or other arene ring. These compounds, noted for their antioxidant capacity, are often synthesized by algae in response to environmental stress: UV light, high salt concentrations, microbial stress, herbivore grazing, etc. (Freile-Pelegrín & Robledo 2013).

Of particular interest are the phlorotannins synthesized by brown algae, a unique class of polymers of phloroglucinol (1,3,5-trihydroxybenzene - Figure 1.4) with unique and characteristic linkages. They possess a unique structure that is not found in terrestrial plants and may constitute up to 25% of the dry weight of brown algae, although their concentration varies with habitat, time of harvest, light-intensity exposure, and nutrient availability (Le Lann et al. 2008; Freile-Pelegrín & Robledo 2013).

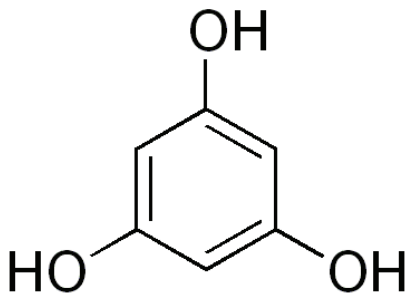

Figure 1.4. Phloroglucinol (Wikimedia Commons)

This antioxidant activity relatively well described. Hydroxyl radical scavenging capacity is closely related to the number of sites in phlorotannins' benzene rings for the addition of hydrogen radicals. Phlorotannins can inhibit linoleic acid oxidation induced by alkane radicals and cannot scavenge superoxide radicals (Xiao et al. 1995). They can also chelate transition metals (Ragan et al. 1979). Degree of polymerization also heavily influences the biological effect of the compounds, with molecular weight being linked notably to antioxidant activity (Xia et al 1995) and grazing deterrents (Boettcher & Targett 1993). Phlorotannins also absorb into the UV range, although on the shoulder of the absorption peak (Pavia et al. 1997) and several authors have postulated that they play a role attenuating UV directly (Guinea et al. 2012; Svobodová et al. 2003).

Phlorotannins exhibit a wide range of biological effects related to their antioxidant role that can be of utility in cosmetics. Free radical scavenging activities will exert electron donors and can react with free radicals to convert them to more stable products, terminate radical chain reactions, and help the relief of inflammatory symptoms caused by harmful radical compounds. This is most notably illustrated in in the case UV exposition and related oxidative stress. UVB-induced oxidative stress including generation of hydroxyl radicals by the Fenton reaction (FeSO4), lipid peroxidation, reduced protein and enzymatic activity in human keratinocytes was prevented or reduced by *S. muticum* extract, which was attributed to the polyphenol content (Piao et al. 2011). Through the action of these combined activities, they effectively reduce cell mortality on exposure to UV, (J. A. Kim et al. 2013; Balboa, Li, et al. 2015).

Phlorotannins and related polyphenols are not limited to antioxidant effects. A polyphenol rich extract of *Turbinara ornata* in India showed inhibition of activity against nine strains of human associated bacteria (Vijayabaskar & Shiyamala 2011). These compounds from brown algae have potential applications in skin care products as antibacterial (Tanniou et al. 2014) or antioxidants (Imbs et al. 2013).

Polyphenols are not restricted to brown algae however: both red and green algae are known to produce such compounds. Polyphenol content was correlated to antioxidant activity as measured by DPPH radical scavenging assay in Chaetomorpha species. The authors of the study observed the highest activity in extracts of C. linum (Farasat et al. 2013). Halogenation or other modification may modify and increase biological activity of this type of molecule, but the phenomenon is the most common in red algae. As an illustration, halogenated phenols from *Polysiphonia* sp have antilipogenic effects (Mikami et al. 2013).

Phlorotannins are more or less readily extractable if the seaweed biomass is properly handled. They are often present in quantity in the extracts relative to other types of bioactive compounds. Water-organic solvent mixtures are particularly suited to the extraction of phlorotannins. Crude extracts are semi-purified and fractionated by separating methods based on both the polarity and the molecular size of compounds (Gall et al. 2015). These molecules are relatively easy to quantify in raw extracts (Stengel & Walker 2015), and this ease of detection may tempt some misattribute observed bioactivity to these compounds. However, they are also relatively fragile, for example a loss of reported antioxidant activity from the phenolic extract of *S. muticum* occurred when drying of took place at temperatures above 40°C (Le Lann et al. 2008).

Proteins and peptides

Seaweeds are rarely promoted for the functional properties of their proteins in comparison to other metabolites (Wijesinghe & Jeon 2012; Harnedy & FitzGerald 2015). This can be explained for several reasons. The protein content of seaweeds is relatively low when compared to polysaccharides or polyphenols. Moreover, extraction of seaweed proteins is relatively difficult due to inaccessibility of proteins within macromolecular cell wall assemblies, cross-linking via disulfide bonds to polysaccharides within these assemblages and high viscosity and ionic interactions arising from cell wall and intra-cellular polysaccharides. These interactions are particularly hindering in brown algae (Wijesinghe & Jeon 2012). The technical difficulties leave them relatively unexplored as compared to other major (and minor) seaweed metabolites.

One of the most prominent examples of seaweed proteins used for, or at least having potential for use in cosmetics are the phycobiliproteins. They are a group of antennae-protein pigments commonly present in cyanobacteria and red algae. Four main classes of phycobiliproteins exist: allophycocyanin (APC, bluish green), phycocyanin (PC, blue), phycoerythrin (PE, purple), and phycoerythrocyanin (PEC, orange). Due to the toxic effect of several synthetic dyes, there is an increasing preference to use natural colors. In this way, C-phycocyanin and R-phycoerythrin have attracted some attention in the cosmetic industry. Moreover, these types of proteins have good antioxidant, anti-inflammatory, antiviral and antitumor activities, those these are not currently commercially exploited. However, extraction is difficult and expensive, which limits the exploitability of these compounds in the sector, although patents are not lacking (Sekar & Chandramohan 2008).

Here, lectins from *Codium,* and *Hypnea* sp are were identified as hemagglunitators (Dinh et al. 2008; Nagano et al. 2005). A *Ulva lactuca*-specific lipopeptide with purported elastase (a MMP) inhibiting properties classed has been patented (Delaunay & Volle 2011). Peptides from *U pinnatifida* are known angiotensin-converting enzyme inhibitors (with a blood pressure lowering effect - Harnedy & Fitzgerald 2011). Two antioxidant peptides, carnosine and glutathione, which are generally present in high concentrations in animal muscle, have been found in macroalgae (Fleurence 2004, Shiu and Lee 2005). On a more general level, protein extracts can have a variety of interesting effects. Uses of algal proteins or derivatives can conferring moisture retention on hair and skin, showing strong affinity with these substrates (Samarakoon & Jeon 2012).

If the technical hurdles could be met, proteins and peptides of seaweed origin may be of particular interest, as over the last decades this type of ingredient been used increasingly in cosmetic formulations (Lintner 2007). Potential bioactive peptides by accessing algae proteins are described by the initiation of proteolytic enzyme-assisted extractions (Figure 1.5- Samarakoon & Jeon 2012).

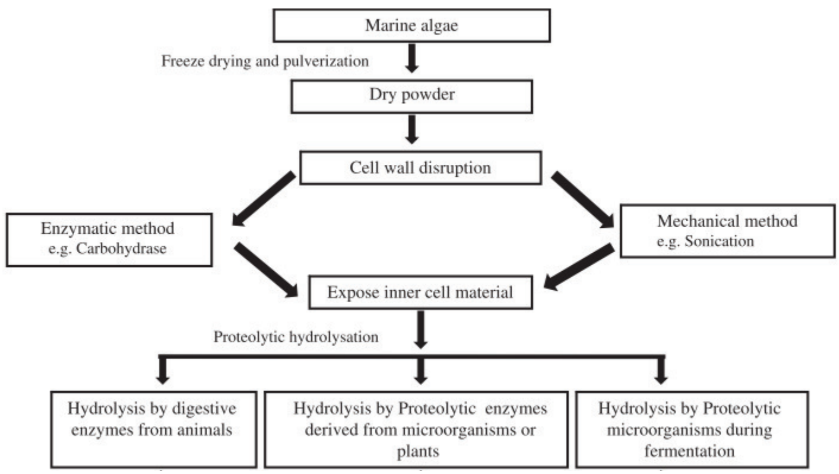

Figure 1.5. Proteolytic hydrolysation of seaweed biomass

Miscellaneous compounds

Besides the classes of compounds described previously, seaweeds produce a very wide variety of organic compounds with many unique and promising properties.

Sargassum species present particularly interesting compounds chromenes derivatives (polycyclic organic compound that results from the fusion of a benzene ring to a heterocyclic pyran ring) for further study, especially concerning their anti-photoaging effects. Sargachromenol from *S. horneri* has been shown to suppress MMPs through the inhibition of TIMP1 and -2 genes (J. A. Kim et al. 2012). A similar tetraprenyltoluquinol meroterpenoid with a chromane moiety, isolated from *S. muticum* by Balboa et al (2015) Figure 1.6. The compound showed photodamage attenuation on irradiated cells with UVA light, presented protection against intracellular ROS generation in a degree comparable to retinoic acid (9.1–20.6%) and did not display toxicity against human dermal fibroblast cell.

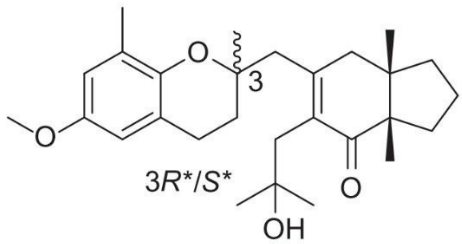

Figure 1.6. Tetraprenylquinol metroterpenoid isolated from S. muticum (Balboa et al. 2015)

The dichloromethane/methanol extract from the red alga *Hypnea musciformis* exhibited PPE elastase inhibition. A diketosteroid, the 20-hydroxy-5α-cholest-22-ene-3,6-dione was responsible for this activity (Bultel-Poncé et al. 2002). Another phycosteroid from *U. lactuca* was shown to have good anti-inflammatory activity in a mouse ear edema assay reaching 72.5% inhibition at 1.5 mg/ ear as well as broad spectrum anti microbial activity (4 species of bacteria, 4 fungi and 4 yeasts) (Awad 2000).

Although generally not containing high quantities of fatty acids and related lipidic compounds, those that are found in macroalgae are often quite distinct. For example in *U. lactuca,* three monounsaturated fatty acid derivatives as active components, a keto-type C18 fatty acid and two derivatives which efficiently activated human antioxidant-response element enzymes (Wang et al. 2013)

Caulerpa species, rather well investigated because of their invasive potential, use in aquaria and culinary interest ("green caviar") have a host of singular molecules. For example, Caulerpenyne, isolated from *C. taxifolia*, shows good 12-Lipoxygenase (12-LO) inhibition, a mediator of the arachidonic acid inflammatory pathway (Nimoniya et al. 2008). The same molecule also shows some antibacterial activity (Smyrniotopoulos et al. 2003). Glycolipids, lipids with a carbohydrate attached by a glycosidic bond, extracted from *C. racemosa* also show antiviral activity against Herpes Simplex Virus (HSV-1) as shown by

(Wang et al. 2007). Characteristic alkaloid Caulerpin is has anti-inflammatory action as well as antinociceptive effects (de Souza et al. 2009).

Several species screened here were shown to contain antibiotic terpenoids e.g. *Asparagopsis* sp bromoform (Paul et al. 2006). The use of some form of antimicrobial compound is often necessary in cosmetics in order to ensure shelf life and limit microbial contamination risks.

Intellectual Property

Overall, queries of individual species names brought up 4344 records, with 53.4% (1986) of all patents filed under the classification #A61K, referring to dermocosmetic applications, affirming cosmetics as one of the major branches of valorization of seaweed biomass. It should be noted that the classification is non-exclusive and may refer to an extraction method that is intended for cosmetic or other use. Many of the patents also refer to 'structuring' components of cosmetics (i.e. jellifying, viscosity controllers, etc.).

The number of patents referring to each species ranged from 0 to 1273 in the case of *Undaria pinnatifida,* the most researched and patented of all of the seaweeds studied. Similarly, the range of patents referring to a dermocosmetic formulation, classed under the code #A61K ranged up to 610 (with *U pinnatifida* again at the top). As such, the species accounted for more than a third of the total patents filed, representing 29% of all the patents examined, in the same way it represented in 27.2% of all dermocosmetic records.

Ulva lactuca, followed suite, with 601 patents in total and 257 in A61K. *U. lactuca*, is widespread throughout the world, and profilerates in large blooms when conditions are right. Due to the difficulty in identifying the species in the genus *Ulva*, IP may actually contain information on several species in the genus.

Finally, another green seaweed, *Codium fragile* was next on the list with 350 patents mentioning it in their full-text, with slightly less than half (174) being filed under the dermocosmetics code.

Species	All	A61K	Species	All	A61K
C. parvulum	0	0	*N. harveyi*	0	0
A. amadelpha	0	0	*W. setacea*	0	0
C. connivens	5	0	*D. japonica*	0	0
C. isthmocladum	0	0	*A. preissi*	0	0
U. australis	70	30	*L. lallemandii*	0	0
U. prolifera	83	32	*S. chordalis*	1	0
C. parvifolia	5	5	*A. spicifera*	3	0
U. lactuca	601	257	*G. vermiculophylla*	19	13
C. aerea	9	5	*G. rugosa*	10	6
C. taxifolia	51	9	*A. taxiformis*	35	27
C. scalpelliformis	4	4	*P. morrowii*	20	13
C. linum	21	12	*G. salicornia*	27	22
U. intestinalis	117	38	*B. hamifera*	19	14
C. cylindracea	125	68	*C. ustulatus*	6	6
C. prolifera	69	49	*K. alvarezii*	46	35
C. fragile fragile	350	174	*G. turuturu*	205	76
S. schimperi	0	0	*A. armata*	127	89
S. fluitans	7	0	*H. musciformis*	148	108
S. natans	106	59			
C. peregrina	2	2			
S. polycystum	28	17			
F. serratus	265	138			
S. muticum	101	60			
Turbinaria ornata	16	11			
F. evanescens	123	76			
S. horneri	247	178			
Undaria pinnatifida	1273	610			

	Total	A61K	Ratio
Chlorophyta	1505	683	45%
Ochrophyta	2168	1151	53%
Rhodophyta	666	409	61%
All	4344	2243	52%

Table 1.7. WIPO patents, A61K patents and PATENTABILITY Index

Due to the sheer number of patents available on the species studied, it was impossible to review all of the claims from the full text results. Thus, some bioactivities may have been overlooked if research was performed in an exclusively commercial setting, even if patents are not peer reviewed and subject to more uncertainty than classic scientific articles. Intellectual property is a very interesting resource, and although not subject to peer-review, represents large quantities of data not always available in scientific journals.

When the search was concentrated to the front page of the patent application, results were much more limited. Indeed this ensured that the specie's name was mentioned in the abstract at least. Just 22 species had at least one patent with their name in the abstract. However, eight of those were not classed in the domain of cosmetics (A61Q). Of the patents covered in the search, the huge majority of applications come from the species native areas, with Japan, Korean and China representing 88% of cumulated patents (Figure

1.7). Even though many of these species are present in a range of territories the cultural use of seaweeds and the large market for cosmetics in Asia seems to favor research in this area. Although much more difficult to quantify this phenomenon is also very visible in the scientific literature, with the overwhelming majority of articles coming from these same countries.

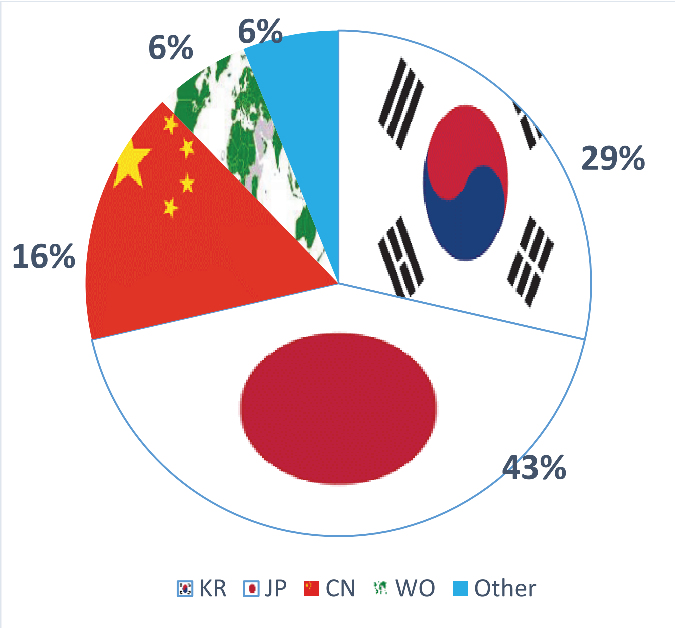

Figure 1.7. Geographic origin of A61Q patents. KR: Korea; JP: Japan; CN: China; WO: World

Most of the patents had several complementary claims (Table 1.8): hydration, anti-aging, anti-inflammatory and no single claim dominates in red and green algae (Figure 1.8). However, anti-aging claims predominate with 16 patents mentioning such effects among

Brown algae, followed by the related antioxidant claim, although with less than half of that total.

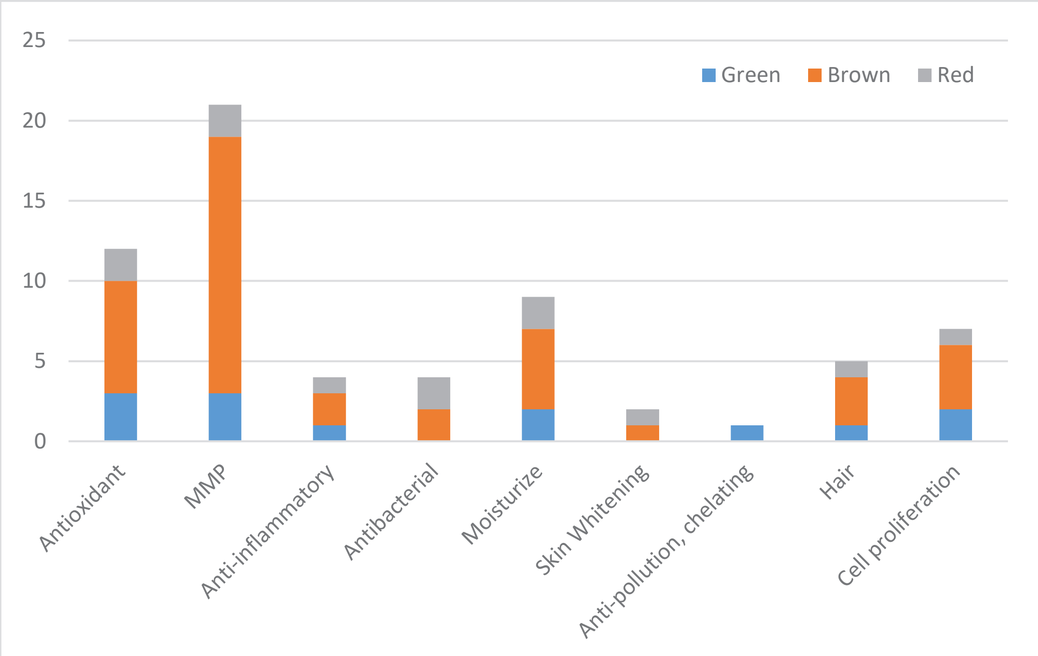

Figure 1.8. Claims of A61Q Patents

Species	Date	Authors	ID Number	Description
Caulerpa brachypus f. parvifolia	2003	Mitusaki, Ito	JP2005139116B2	NMF promoting factor
Codium fragile fragile	2016	Kim, Hyeon Chung	KR1020160030615 A	Composition for blocking fine dust which prevents skin diseases; Ulvan
	2012	Kim, Hyeon Chung	KR1020120056594	Antioxidation, skin elasticity, and anti-wrinkling
	2012	Park, Eun Kyung	KR1020120026308 B1	Antioxidation, cell proliferation, collagen synthesis and skin moisturizing
	2008	Hiroshi, Tanaka	JP2008239493A	Keratinocyte differentiation promoters; anti-inflammation
	2003	Hibino, Toshihiko	JP2003081861A	Prevent the hair loss and promote hair growth
Ulva lactuca	2010	Montaria, Daniella	EP2148651A2	Cosmetic composition with a lifting effect for sustaining relaxed skin tissues and reducing their sagging
Ulva prolifera	2010	Wook-Jae, Lee	KR1020100031253 B2	Anti-inflammatory composition; inhibition of NO generation, Inflammatory Cytokine Generation and PGE2 generation
Fucus evanescens	2012	Tsutomu, Fujimura	JP2011266104A	Collagen gel shrinkage promoter
	2008	Hidenori, Komai	JP2008069133	Composition for slimming body
	2001	Tsutomu, Fujimura	JP2001278769A	Integrin stimulating, skin- tightening effect
Fucus serratus	2011	Baldrich-Serra, Noemi	WO/2011/147933	Skin care agent, skin barrier recovery agent, and moisturizer
	2014	Qi, Xiang	CN103976907A	Anti-allergenic
Sargassum horneri	2015	Park, Gwee Kyo	KR1020150062625 A	Alleviating skin wrinkles, moisturizing skin, improving skin elasticity, reinforcing a skin texture, and ensuring anti-oxidative activities
	2014	Seoul, Cai Chun	CN103860425B	Antioxidant, collagen stimulant, moisture retention, skin elasticity
	2014	Seoul, Cai Chun	CN103720620B	Moistruising, MMP inhibition
	2014	Seoul, Cai Chun	CN103720619B	Moistruising, MMP inhibition, whitening
	2013	Kim, Se-Kwon	US20130338221A 1	Chromene containing anti photoaging (MMP inhibiting)

	2009	Sadayoshi, Akizuki	JP2009263644A	Soap containing fucoidan
	2009	Hideaki, Megata	JP2009242325A	Apoptosis inhibitor
	2009	Kim, Yong Kee	KR1020090027387	MMP Inhibition, Collagen stimulation
	2008	Hiroshi, Taguchi	JP2008056643A	Antioxidant, chelating agent, metabolic stimulator
	2007	Hiromi, Arakawa	JP2007119384A	Hyaluronidase inhibition
Sargassum muticum Undaria pinnatifida	2011	Hyun, Chang Gu	KR1020110115803 B1	Promotion of collagen
	2010	Kim, Hyeon Chung	KR1020120056594 A	Composition for blocking fine dust which prevents skin diseases; Ulvan
	2010	Kim, Hyeon Chung	KR1020120026308 B1	Antioxidation, skin elasticity, and anti-wrinkling
	2007	Park, Eun Kyung	JP2008239493A	Antioxidation, cell proliferation, collagen synthesis and skin moisturizing
	2015	Moon, Woi Sook	WO2015099280A1	Antioxidative, anti-inflammatory, and anti-atopic
	2015	Panpan, Yang	CN104323976A	Skin tightening effect
	2013	Ayaka, Takashi	JP2013010693A	MITF-M production promoter
	2012	Kim, Moo Young	KR1020120077271 B1	Eyebrow/ Eyelash growth enhancer
	2011	Kim, Moo Young	KR1020110075626 B1	Enhance skin regeneration ability and to ensure persistence
	2011	Park, Kwon Pil	KR1020110023261 B1	Antioxidation - Fucoidan
	2010	Minhui, Wan	CN101816624B	Protective barrier, moisturizing
	2010	Otero, Carmen	ES2335333B1	Vitamin and mineral rich
	2007	Iovanni, Carl	WO2007119227	Depilatory/ Epilatory cream
	2002	Yukinori, Takahashi	JP2002012552A	Immune function stimulation, and preventing and treating effects for infectious diseases, skin diseases and anti-tumor effect
	2001	Norihisa, Kawai	JP2001181167 A	Elastase inhibitor

	2000	Joji, Yamahara	JP2000344678A	Inorganic seaweed ash-based antimicrobial agent
	1999	Chin, Shim Ho	JP11217317B2	Sebum blocking, accelerating blood circulation
Asparagopsis armata	2014	He, Wang	CN104000769A	Anti-acne face cream
	2014	He, Wang	CN103976930A	Anti-glycation
	2009	Takahiko, Ikeda	JP2009196969A	Cell activation, anti-inflammatory action, and antibacterial activity,
Bonnemaisonia hamifera	2013	Hyun, Jin Won	KR1020130103185 B1	Suppression of UV-induced apoptosis
Hypnea musciformis	2013	Braga, Simone	BRPI1003158A2	Hair restructuring
Kappaphycus alvarezii	2002	Masato, Izume	JP2002193736A	Hydration and smoothness to the skin
	2002	Hiroshi, Hoshino	JP2002193737B2	Skin bleaching
Gracilaria vermiculophylla	2015	Park, Gwee Kyo	KR1020150062625 A	Alleviating skin wrinkles, moisturizing skin, improving skin elasticity, reinforcing a skin texture, and ensuring anti-oxidative activities
	2011	Hiroyki, Kobayashi	JP2011079769A	Hydration
	2001	Norihisa, Kawai	JP2001302491A	Skin whitening

Table 1.8. A61Q Patents and Claims

Genre/ Species	Supplier	Product name	INCI	Advertised activity
Caulerpa	Gelyma	Okinacea®	Aqua (and) Caulerpa Extract (and) Hydrolyzed Rice Bran Protein	Stimulates collagen IV and laminin-5
Codium	SEPPIC	Codiavelane® BG PF	Propylene Glycol (and) Aqua (and) Codium fragile Extract	Immediate and long lasting hydration
	Gelyma	Mirual	Aqua (and) Algae Extract	Functions as a marine moisturizer and cell protector.
Ulva	Lipotec S.A.U.	ACTIPHYTE ™ sea lettuce	Glycerin (and) Water (and) Ulva Lactuca Extract (and) Phenoxyethanol	Radical scavenging and anti-inflammatory agent
	Greentech	QT 40®	Glycerin (and) Aqua (and) Hydrolyzed Ulva Lactuca Extract	Re-sculpt and re-model facial contours: it improves firmness, elasticity, density and decreases skin sagging
	Greentech	PHYTELENE COMPLEX EGX 773 BG Dry Skin	Butylene Glycol (and) Aqua (and) Chondrus Crispus Extract (and) Ulva Lactuca Extract (and) Enteromorpha compressa Extract (and) Palmaria Palmata Extract (and) Undaria Pinnatifida Extract	Deep moisturizing formulations and particularly for introduction in after-sun or anti-aging formulas.
	SEPPIC	Phycol UL®	Aqua (and) Propylene Glycol (and) Ulva Lactuca Extract	Detoxify the skin as it has anti pollution properties
*Fucus serratus**	Lucas Meyer Cosmetics	Homeosta-SEA™ Homeo-Shield™	Fucus serratus extract (and) Glycerin	Transglutaminase activity leading to the maturation of cornified envelope – enhancing of the skins barrier function
	Lucas Meyer Cosmetics	Homeosta-SEA™ Homeo-Soothe™	Fucus serratus extract (and) Glycerin	PGE2 inhibitor, reducing the inflammatory response and

	Gelyma	SEAVIE®	Aqua (and) *Fucus serratus* Extract	producing a soothing effect Mineral enrichment of skin
Sargassum muticum	Gelyma	Phyactyl	Aqua (and) Sargassum Muticum Extract	Mineral rich, antioxidant
Undaria pinnatifida	The Garden of Natural Solution Co., Ltd.	MYFerm	Undaria Pinnatifida Extract (and) Lactobacillus Ferment	Increase collagen synthesis
	Biocosmethic	Wakame Extract PGW - BCE4028	Propylene Glycol (and) Aqua (and) Undaria Pinnatifida Extract	Not stated
	SEPPIC	EPHEMER®	Caprylic/Capric Triglyceride (and) Undaria Pinnatifida Extract	Immediate (24 hours) and long lasting (8 days) antioxidant effect
	Gelyma	Kimarine®	Aqua (and) Undaria Pinnatifida Extract	Low molecular fraction that ensures biological protection of the skin against reactive oxygen species
	Lipotec S.A.U.	ACTIPHYTE ™ wakame	Water (and) Undaria Pinnatifida Extract (and) Phenoxyethanol	Reduce pigmentation, and therefore it is expected to possess skin-brightening effects.
	Greentech	PHYTELENE EG 755 BG Wakame	Butylene Glycol (and) Aqua (and) Undaria Pinnatifida Extract	Multiple properties and more specifically regenerating
	SEPPIC	Phycol UP®	Aqua (and) Propylene Glycol (and) Undaria Pinnatifida Extract	Water soluble extract which acts as an energetic cocktail for the skin
	Greentech	PHYTELENE COMPLEX EGX 773 BG Dry Skin	Butylene Glycol (and) Aqua (and) Chondrus Crispus Extract (and) Ulva Lactuca Extract (and) Enteromorpha compressa Extract (and) Palmaria Palmata Extract (and) Undaria Pinnatifida Extract	Deep moisturizing formulations and particularly for introduction in after-sun or anti-aging formulas.

		PHYTELENE COMPLEX EGX 771 BG Hair Conditioning	utylene Glycol (and) Aqua (and) Chondrus Crispus Extract (and) Ascophyllum Nodosum Extract (and) Palmaria Palmata Extract (and) Laminaria Saccharina Extract (and) Undaria Pinnatifida Extract	Restore beneficial conditions for the health of hair.
Asparagopsis	Lucas Meyer Cosmetics	Aldavine™ 5X	Ascophyllum Nodosum Extract (and) Asparagopsis Armata Extract	Normalizes the excessive increase of microcirculation caused by UV exposure, preventing premature aging, thus increasing skin elasticity & resiliency. It has also a significant action in the reduction of the appearance of dark circles and under eye bags
	Algues et Mer	Ysaline®	Asparagopsis armata extract	Preservative, antibacterial and antifungal
Hypnea musciformis	Chemyunion	Hidrahair Sphere	Polyquaternium-7 (and) Hypnea Musciformis Extract (and) Atelocollagen (and) Glycosaminoglycans (and) Hydroxypropyltrimonium Hydrolyzed Wheat Protein (and) Retinyl Palmitate (and) Tocopheryl Acetate (and) Pantothenic Acid	Hair upkeep
	SEPPIC	Biorestorer PF	Water (and) Butylene Glycol (and) Hypnea Musciformis Extract	Restructures and smoothes the hair, bringing it back to a more normal state.
Kappaphycus alvarezii	Gelyma	Sea Moist Complex	Glycerin (and) Aqua (and) Kappaphycus Alvarezii Extract (and) Sea Water	Extremely potent moisturizer for dry skin and provides the skin with its ideal level of moisture and nutritive minerals for up 24 hours.

Gracilaria	Aqia	BIOEXTRACT ALGAS GRACILARIA HG	Algae extract	Emollient, derma protector, hydrating, soothing, restorative, nutritive. Confers shine, volume and softness to hair.

Table 1.9. Commercial seaweed extracts for cosmetic ingredients

Despite the high numbers of species and patents described here, only 10 species are actually commercialized as bioactive ingredients in skin care products in Europe (Table 1.9), divided fairly even along the broad divisions of seaweeds. Mirroring results in most of the other indexes, *U. pinnatifida* is the most present, with six companies offering nine different extracts. Next, again mirroring the patent data comes *Ulva lactuca*. Again, there is no clear 'star' in the Red Algae, as seen previously.

The breakdown of uses for these products is shown in Figure 1.9, with hydration being the principal use for the seaweed extracts. The excipients, as well as the polysaccharides, concentrated minerals and other metabolites can all contribute to a hygroscopic effect. This type of ingredient can be used in many types of cosmetic formulas: skincare and sun care products alike. This versatility along with the green image and popularity of natural, ocean-based ingredients may drive the demand for this type of extract. Several interesting remarks can be made here: most of these extracts are promoted for their MMP inhibiting potential or activity promoting collagen production. Other claims such as "energizing" skin cells are hard to determine, and very marketing oriented.

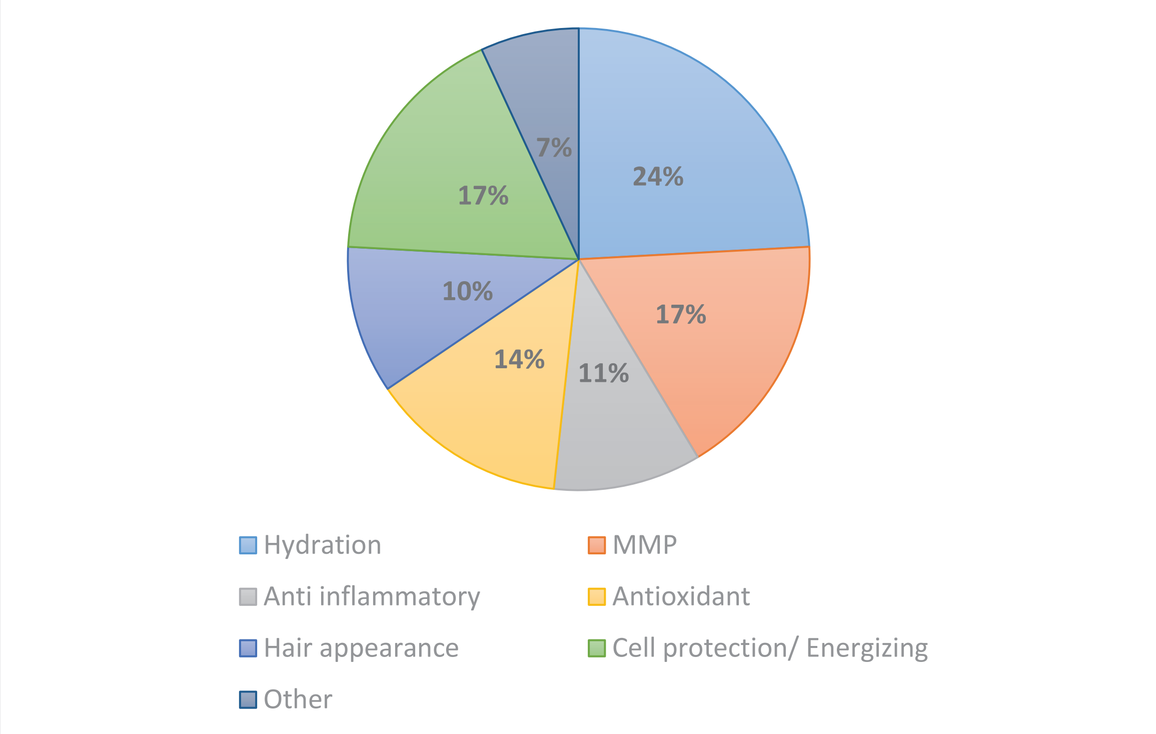

Figure 1.9. Claims for on-market seaweed derived cosmetics ingredients (note MMP regroups anti-aging claims)

Most are sold solubilized in glycerin or aqueous mediums. Glycerin and propylene glycol can be either direct extraction solvents, or secondary liquid excipients for for vacuum evaporated organic extracts. These compounds further present the advantages of being hygroscopic, bacteriostatic and skin permeability enhancing, ensuring good performance of solubilized compounds (García, J. I.; García-Marín, H.; Pires 2014; Björklund et al. 2013).

The most and least studied species

From this study, several important factors stood out. First, temperate species received more attention than tropical ones, with the exception of the carragheenophytes and Caulerpa species. Moreover, some groups are very prominent whereas others are entirely neglected.

Green algae can be especially difficult to indentify based on morphological features alone. Besides *U lactuca*, the family Ulvaceae is relatively poorly studied: perhaps due to the difficulty of identification. In this type of genus, where species are described with global repartition, cryptic diversity should be expected. Indeed, a recent survey of New Zealand waters uncovered 5 species of *Ulva* (including *U. lactuca*) and related *Umbraulva* from overseas, and 3 local species that were unidentifiable on morphological characteristics alone (Heesch et al. 2009). These species, known for their bloom forming characteristics, could be an unexpected source of biological material, especially when one takes into consideration the numerous bioactivities of *U. lactuca* extracts.

Studies concerning the order of Ceramiales reveal wide genetic and morphological diversity and correspondingly high diversity in biological activities and secondary metabolites. However, they are least investigated of the invasive species in terms of the biological activities that their extracts may present. The greatest quantity and diversity of small halogenated phenolic compounds of all red and brown seaweeds occurs in members of the family Rhodomelaceae (Kladi et al. 2004), including many other unusual metabolites that may present extremely interesting properties, including potent cytotoxicity and neuroreceptor binding (Gross et al. 2006). Even if the relatively high profile species examined here were not studied, these small species showed the 3rd highest antioxidant capacity (FRAP method) out of 30 species screened in Hawaiian waters (Kelman et al. 2012). Some families and genera have been studied in detail; other species-rich taxa are still waiting for a comprehensive molecular reassessment (e.g., the genus *Polysiphonia*). It would seem that their small size and epiphytic nature make identification difficult, not to mention obtaining significant quantities of raw material. Harvesting may also be problematic because of their fragile nature and the vegetative reproduction capacities of many of the quicker to spread species.

The Bonnemaisoniales are another family of seaweeds reputed for their abundant secondary metabolites. *Asparagopsis armata* is notably cultivated in Ireland and Brittany, France for use in the cosmetics industry (Katsanevakis et al. 2014b) but *Asparagopsis taxifolia* and *Bonnemaisonia hamifera* also have proven qualities as raw material. PS in this group are mainly studied for their effect on blood coagulation (Manilal et al. 2010; Caporiccio et al. 1984) and antiviral activity (Haslin et al. 2001). The family is well known for the numerous halogenated compounds it contains, and that continue to be discovered (Kladi et al. 2004; Greff et al. 2014). These compounds are extremely potent antibacterial and antifungals, as well as powerful enzyme inhibitors, all characteristics that can help their integration into cosmetic formulas as preservatives. Others also show photoprotective effects against UV-B exposure (Piao et al. 2012; Hyun et al. 2012). MAA are known to be present in the family, notably Shinorine, Palythine and Porphyra 334, with concentration fluctuating according to UVR exposure as well as dissolved nitrogen load (Gröniger et al. 2000; Figueroa et al. 2008).

Environmental considerations and impact on resource use

Due to their high profile and abundance, invasive species are often investigated for potential ways to revalorize their biomass. Indeed, for the most part, information on the biological activity of various extracts of macroalgae is much more abundant than information concerning their invasive properties. Exploitation of invasive seaweed is commonly proposed as a way to slow/ control their spread (for example Vaz-Pinto et al. 2014; Milledge et al. 2015). Indeed, it is well known that many metabolites valuable in the cosmetics industry are present – and currently exploited – in seaweeds (Cardozo et al. 2007; Bedoux et al. 2014).

Using wild stocks of seaweeds to extract compounds requires a certain rigor in periods and conditions of harvest. Various metabolites vary with geography and seasonality, so these are extremely important aspects to take in consideration, as evidenced by a wealth of data (Fung et al. 2013; Tanniou et al. 2014; Harnedy & Fitzgerald 2011; Padilla-Gamiño & Carpenter 2007). The seaweeds that wash up on shorelines are almost systematically mixes of many different species. As such, drift biomass may not be the best source of raw material, but with proper care and study, revalorization of this “nuisance” is a real possibility. This could be a limiting factor to the exploitation of wild invasive species, especially if the active compounds are scarce, care would have to be taken to control harvest conditions in order to optimize yields. However modern preservation technics: lyophilization, dehydration, deep freezing, etc. can alleviate somewhat a lack of regularity if demand exists.

Cultivation could be an option, if the species has already been deemed established to the region in question and not subject to active eradication efforts. Seaweed aquaculture accounted for almost 50% of global mariculture production and satisfies 96% of global demand (Cottier-Cook et al. 2015). The benefits of this kind of exploitation are obvious in terms of control of production: biomass can be controlled and monitored in quantity and quality. Recent trends in seaweed cultivation are pointing the sector towards high value secondary metabolites, traditionally seaweeds being exploited for their polysaccharides most notably. Associating seaweed culture with pisciculture and/shellfish culture in IMTA systems is a proven way to reduce the ecological impact of aquaculture. Filter feeders assimilate particulate waste from the fish, and algal growth is stimulated by the dissolved nutrient load. Moreover, it can increase yields of valuable compounds such as MAAs and phycobiliproteins in seaweeds (Figueroa et al. 2008; Figueroa et al. 2012). However, it is also a major vector for the introduction of foreign species and great care must be taken to avoid unforeseen ecological consequences. The introduction of aquaculture species such as *Kappaphycus* in a futile attempt at starting a carrageenan industry in Hawaii has had strong localized impacts (Ask et al. 2003). In the same manner, although inadvertent the introduction of *U. pinnatifida* has had wide implications in Europe (Stiger-Pouvreau & Thouzeau 2015).

The other option is regular control in a defined area: this would be similar to a classic wild harvest. Paradoxically, the more successful of a seaweed ‘invasion’ is in this case the better, even if the management effort is set to control it. An example of an abundant and completely undeveloped resource are *S. fluitans* and *S. natans*, which have become nuisances in the Caribbean and off of African coasts after huge blooms in the last decade, with exceptional strandings on popular tourist beaches in Mexico and across the Caribbean (Lewis 2015).

Sustainable commercialization will benefit greatly from the “green” image of harvest; it is thus preferable not to be seen as the introducer of a pest. In any case, negative public perception towards these species in an ecological sense is an important factor for the commercialization of derived products. Invasive species are prominent in their abundance and regulation of their biomass may be encouraged by policy makers in the form of subventions and/ or tax breaks. Contributing to control/ eradication programs could be a beneficial situation to all of the parties involved: it can offset costs of public effort while helping local ecosystems, while rendering a valuable by-product. Furthermore, companies can vaunt their commitment to sustainable development. Finally, wild harvested seaweeds can be certified organic (if grown in good ecological conditions), which raises their market value and that of their derived products (Cervellon et al. 2012).

Cosmetic products may be a viable option to revalorize otherwise to be discarded biomass: the long-term viability of the resulting industry depends on the targets of the management program. If the program seeks to eradicate a species completely, the product could eventually be sold to manufacturers already processing biomass of the same species from different sources. The ‘control effort’ raw biomass would have the advantage of having little direct production costs inherent to aquaculture (maintaining equipment, salaries, etc.), and could help offset the costs of the control effort (boats, petrol, etc.). However, extra care must be taken for many species to ensure that the control effort does not actively encourage spreading. For example, harvesting of *Caulerpa* is a delicate operation that should be performed with great care and only by well- trained personnel, due to risks of propagation by fragmentation (Rindi, Soler-vila, et al. 2012), indeed it has been suggested to ban commerce of live specimens of the genus because of the risks of accidental introduction (Stam et al. 2006).

In any case, if patent data is indicative of industrial interest, invasive seaweeds have still largely failed to inspire western companies in their newly colonized areas. The number of species commercialized is inferior to that of the species with intellectual property concerning their use in cosmetics. However, all of the commercialized species are subject to patents in Japan, Korea and China. As such, patents can be a very good source of information, along with research articles to indicate direction and potential uses of seaweeds. Looking into phylogenic information, the species that are in the same genus as more "exploited" ones: notably *Codium isthmocladum* or some of the many species of *Caulerpa* present a definite opportunity in that other species in the same genus are known to produce valuable metabolites (*C. fragile* and *A. armata* respectively).

Commercial application

Cosmetics, according to their legal definition in the European Union are "any substance or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odors and/or protecting them or keeping them in good condition" (No 1223/2009 2009). This is a major challenge for the commercialization of many compounds listed in this review, and for good reason: haphazard manipulation of cellular function can have unforeseen consequences. However, this definition does allow for changing appearance, protecting and keeping in good condition. If a product is destined for one of the above applications and does not show undesirable activity in a range of tolerance tests, it may be admitted for sale.

According to the above regulations, the best fit in cosmetics *stricu sensu* among the bioactivities screened here are in the domains of antioxidant activity, MMP inhibition and UV protection. These do not obligatorily act on cellular or enzymatic activity to be active, thus can comfortably enhance cosmetics formulas without cause for concern. Sunscreen agents cannot be used stand alone in the Europe Union nor can a product be marked as having an SPF if the product does not in fact contain a pre-approved filter. Seaweed extracts may supplement protective activity namely by stopping oxidative stress and the formation of free radicals at membrane interfaces, slowing extracellular matrix metalloproteinase activity and providing UV protection. Playing a role in both intrinsic and photo-aging, extracellular epidermal MMPs are at the heart of many “anti-aging” claims by targeting the mechanism directly responsible for the apparition of undesirable wrinkles.

As a more indirectly functional role, measured antibiotic activity is also a good potential use of seaweed extracts in cosmetics. Currently, preservatives are major source of consumer worry: some have been shown to have irritant effects on skin and potentially more dangerous side effects. Broad-spectrum bacteriostatic algae extracts could have great utility in preserving the formula from microbial contamination. Many of these could be developed into antiseptics and cleansing agents, but their antibiotic activity *in vivo* may be limited by toxic effects (Smit 2004). Use as preservatives for topical applications is a good compromise if the molecule is stable, penetration is slight and it does not show irritant effects. An example of such a product are bromated flavonoids extracted from *A. armata*, currently cultivated in Brittany, France (outside of its natural range) for this reason among others (see Algues et Mer in Table 1.9. Commercial seaweed extracts for cosmetic ingredients). In a similar fashion, Egyptian *U. lactuca* organic extracts were determined to have good characteristics for this type of use (Abd El-Baky et al. 2008). Particularly in the field of natural and “organic” labelled cosmetics, bacteriostatic extracts could be quite valuable because of the lack of available ingredients of the type.

The economics of fine metabolite extraction is not advantageous for most seaweeds, at least for cosmetic use. Most existing seaweed harvesting and current cultivation techniques have been developed for producing commoditized biomass, and may not necessarily be optimized for the production of valuable bioactive compounds (Hafting et al. 2015). Compounds that are only present in fractions of a percentile of the dry weight of seaweed biomass pose serious challenges for efficient and economically viable extraction. For this reason, most if not all of the commercialized seaweed extracts are simple aqueous or organic solvent extractions Table 1.9. Environmental variability is a key factor, and many types of metabolites including polyphenols (Hoyer et al. 2001) and MAAs (Singh et al. 2008), and will greatly influence the yields upon harvest. Care must be taken to ensure that the environmental conditions are optimal at harvest to ensure high quantities of selected compounds. Such organization is not always possible, especially in an on demand production cycle.

Strategies that cosmetic companies can use to create highly active and targeted extracts without rendering the ingredient too expensive are very similar to those used while screening extracts. The use of low-cost, organic or aqueous solvents can be efficient, especially when simple factors such as temperature and pH are tightly controlled.

Combining this with molecular cut-off techniques can also be useful to obtain higher purity, targeted extracts. In this way many polysaccharides and high weight polyphenols in different seaweeds can be isolated: moreover they often show good antioxidant activity and help cells to cope with UV radiation (Hagerman et al. 1998; Athukorala et al. 2007). Moreover, this type of compound can easily be incorporated into a cosmetic formula without risk of penetration into deeper layers of the skin. Compounds in the filtrate include amino acids, oligosaccharides, mineral salts and other osmolytes.

One very promising perspective is the complete use of biomass, generating several revenue streams. *Sargassum muticum* is a particularly good example of this, with many types of potential uses (Milledge et al. 2015). Balboa et al. have published extensive research on different eco-friendly methods for extraction of fucoidan (2013), antioxidant crude extracts (Balboa, Conde, et al. 2013; Dominguez et al. 2014). They also proposed the extraction of a novel UVA damage attenuating metroterpenoid from the seaweed (Balboa, Li, et al. 2015), through a more elaborate isolation steps to show said effect. Finally, a method for complete utilization of the biomass in a bio refinery concept was developed (Balboa, Moure, et al. 2015) with a particular emphasis on cosmetic applications. In India, Baghel et al. (2015) demonstrated that co-production of several types of products, to completely use up the feedstock was possible, producing bioethanol, higher quality agar than previous types of treatment, pigments and more from *Gracilaria* species.

An avenue for future development of seaweed biomass is also the use in “green” manufacturing processes applied to the cosmetics industry. Seaweeds have long been proposed as potential heavy metal biosorbents for heavy metals from industrial effluent (Bailey et al. 1999). This capacity was more recently put to use to produce nanoparticles (Sharma et al. 2015). Another good example of this is the work of Azizi et al. 2014 who used *S muticum* polysaccharides to make ZnO NPs, which are widely used as mineral UV screens in the cosmetics industry. Fucoidan from brown algae appears to be the best for this process in the current state of the art (Nagarajan & Kuppusamy 2013). The affinity of alginates for divalent cations (Pb^{2+},Cu^{2+},Cd^{2+},Zn^{2+},Ca^{2+}, etc.) increases along with its gluronic acid content (Davis et al. 2003). Using algal PS with different monosaccharide ratios may permit the control of the size of nanoparticles, and merits further study. Finally, the polysaccharides, proteins and lipids present in the algal membranes act as capping agents and thus limit the use of non-biodegradable commercial surfactants that are difficult to remove after the synthesis of NPs (Sharma et al. 2015). Using algal biomass may be effective and “green” method of producing ready to use mineral UV screens for use in cosmetics.

Invasive species are a challenging, yet high-potential biomass for use in cosmetics. Species that can be readily identified an easily sourced, will be the easiest to valorize. The question whether or not biomass can be sustainably harvested comes down to how governmental efforts on managing the spread, or eradicating species. There is no doubt that most contain at least one characteristic that can be marketed in a cosmetic formula, the main incentive here is economics and efficacy of extraction techniques.

Taking into light the above constraints and challenges, a few species stood out for either the abundance, or complete lack of data. On the one hand, species such as *U. pinnatifida* and *U. lactuca* are extremely well studied, providing a substantial background for engineers and formulating chemists. Much of the intellectual property is concentrated in Asia: European companies or indeed universities can mine IP databases for information on extraction techniques as well as be guided towards novel research goals.

4. General Conclusions

Invasive species are a challenging, yet high-potential biomass for use in cosmetics. This is apparent for several reasons, not in the least the prevalence of certain biological characterisitcs: high growth rates and large individual sizes; vegetative propagation; high levels of sexual reproduction and high fecundity; parthenogenetic reproduction and broad environmental tolerances. Moreover, many are already cultivated in or outside of their native ranges as foods or phycocolloids. When they are introduced outside of their ranges, they can have an array of negative effects, monopolizing space, reducing the available habtitat and sources of alimentation for other seaweeds as well as fish species. Even if realatively rarely quantified, these can result in negative effects for local economies.

Newly introduced species are generally seen as nuisances in the public eye, and managers err to the side of caution when these species arrive. Containment efforts can result in a source of cheap and abundant biomass. Species that can be readily identified an easily harvested are by far the easiest to develop into marketable products for local economies. There is no doubt that most seaweeds contain at least one characteristic that can be used in a cosmetic formula.

Cosmetic products may be a viable option to add value to an otherwise to be discarded biomass. Waste or surplus biomass has the advantage of not necessitating the upkeep of farming sites. However, using wild stocks of seaweeds to extract compounds requires a certain rigor in periods and conditions of harvest that may not be optimal when containment is undertaken. Relative amounts of metabolites often vary with geography and seasonality, so environmental variability is an important aspect to take in consideration. However modern preservation technics: lyophilization, dehydration, deep freezing, etc. may alleviate a lack of regularity if demand exists: the long-term viability of the resulting industry depends on the targets of the management program. The availability of seaweed stocks and the capacity to harvest them efficiently is a key, make or break point for the use of their biomass.

In order to be put on the market as active indgredients, seaweed extracts must be investigated for specific types of bioactivity. From an economical, legislative and common sense standpoint, it is best to screen for and promote some more than others. Cosmetics must act uniquely on the surface of the skin and not intercellularly in Europe to avoid being classed as drugs. As such, antioxidant activity, UV protection, matrix-metalloproteinase can all be valid 'active' ingredients for the benefit of the skin, for example to reduce external signs of aging. Antimicrobial activity could also be used, to both preserve fomulas and control microbial growth on the surface of the skin.

Many very promising and indeed already used molecules in the cosmetics industry come from seaweeds. Each major class of seaweeds produces material that can be used for different reasons. Compounds that only represent a fraction the dry weight of seaweed biomass pose serious challenges for efficient and economically viable extraction. Most, if not all of the commercialized seaweed extracts are simple aqueous or organic solvent extractions. Strategies that cosmetic companies can use to create highly active and targeted extracts without rendering the ingredient too expensive are very similar to those used while screening extracts. The use of low-cost, organic or aqueous solvents can be efficient, especially when simple factors such as temperature and pH are tightly controlled. Combining this with molecular cut-off techniques can also be useful to obtain higher purity, targeted extracts.

Indeed, reviewing patent data and commercial availability of seaweed extracts for the cosmetic market confirms the potential and viability of some kinds of applications. Most of these extracts are promoted for skin conditioning effects; that have to do with the hygroscopic nature of extracs, but also their MMP inhibiting potential or activity promoting collagen production. Reflecting the geographical origins of many of the species screened here, much of the intellectual property is concentrated in Asia: European companies or indeed universities can mine IP databases for information on extraction techniques as well as be guided towards novel research goals.

Certain species have received much more attention than others, due to their traditional uses and/ or their capacity to spread. Two species stand out: *Undaria pinnatafida, Ulva lactuca,* for the amount of research and intellectual property that concern them, with large amounts of articles, patents and products on the market derived from them. On the other side of the coin, studies on the order of Ceramiales (Rhodophyta) reveal wide genetic and morphological diversity, and correspondingly high diversity in biological activities and secondary metabolites but the specific species investigated here are not looked at all. In the patent data search, a minority of species had no industry interest as expressed by intellectual property. If patent data is indicative of industrial interest, then it can be said that invasive seaweeds have still largely failed to inspire western companies in their newly colonized areas. The number of species commercialized is slightly inferior to that of the species with intellectual property concerning their use in cosmetics. Patents can be a very good source of information, along with research articles to indicate direction and potential uses of seaweeds.

In the experimental section, two brown algae *Undaria* and *Sargassum* are brown algae, rich in fucoidan, fucoxanthin and polpyphenolic compounds for good antioxidant and MMP inhibiting activities.

U. pinnatifida is one of the more widespread invasive species, worldwide in temperate waters. It was spread by many different vectors, intentionally and not. Moreover, it is highly valued as a food source and is exploited for this reason. Extracts of the seaweed have been shown to display a range of different bioactivities due to the presence of specific compounds. Here we used colorimetric techniques to determine the amounts of different indicator metabolites. As can be expected, amounts varied according to the different producers of seaweeds and their treatment methods. Distilled water effectively extracted alginates, glycerol was able to solubilize a balance of polyphenols and alginates, whereas ethanol effectively extracted polyphenols. Going further, it would be interesting to test for fucoxanthin, depending on suppliers and to devise better extraction methods using an experimental design approach.

Sargassum muticum (Yendo) Fensholt (1955) is one of the more high profile invasive seaweeds in Europe. Many different studies have explored ways to use its polyphenols, which show good antioxidant and anti-UV properties. Ethanol and glycerol were used to extract these compounds, and both types of extracts were examined for antioxidant activity. Glycerol showed both better extraction efficiency and antioxidant activity. Possible next steps in the extraction could thus be fractioning through ultracentrifugation and analysis of DPPH or other antioxidant activity in function of different molecular size weight cut-offs. Given the good antioxidant characteristics of the glycerol extract, it can be a good candidate for a skin protective ingredient.

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Project Report for obtaining the Master's Degree in Marine Resources Biotechnology

Masters project carried out under the guidance of Doctor Francois Sieber and co-supervision of Doctor Clelia Alfonso Neves

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