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Mini review

Marine fungi: An untapped bioresource for future cosmeceuticals

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ABSTRACT

A number of useful metabolites with cosmeceutical potential have been reported from marine sources over the last several years. Marine life, particularly sponge, algae, tunicates, bacteria and fungi, produces a wide variety of bioactive metabolites whose diversity is enhanced by the varied environmental conditions present in the oceans. The marine environment has a large biological and chemical diversity and serves as a source of novel chemical entities with potential industrial application, including pharmaceuticals, cosmetics, nutraceuticals, and agrochemicals. Marine fungi represent a relatively untapped bioresource for novel natural product discovery, although over the past decade marine fungi have providing a number of new secondary metabolites. These secondary metabolites isolated from marine fungi have been used in a range of applications, including cosmeceutical application such as anti-ageing, skin-whitening and anti-acne. In addition, a number of lead compounds have been identified from marine fungi for further development as cosmeceuticals. This review article aims to summarize studies on marine fungal secondary metabolites for application in skin health and cosmeceuticals.

1. Introduction

Nature provides a high diversity of pharmacologically active biomolecules. These natural products are important as leads for the development of novel pharmaceuticals, nutraceuticals and cosmeceuticals. The marine ecosystem covers about 70% of the earth's surface and is extraordinarily rich in biological diversity, particularly in tropical environments. According to the Global Biodiversity Assessment by the United Nations Environment Program, the oceans consist of 178,000 marine species across 34 phyla (Mitra and Zaman, 2016). Marine organisms comprise approximately half of the total biodiversity on earth and produce a wide range of novel biomolecules (Jimeno et al., 2004; Vignesh et al., 2011). Between 1989–2002 around 60% of FDA approved drugs and pre-NDA (New Drug Application) candidates were obtained from the natural environment (Chin et al., 2006; Grabley and Thiericke, 1998). In the past 50 years, exploration of marine bioresources for their unique natural products has been an important area of research. Of the estimated 270,000 known natural products, 30,000 compounds have been obtained from marine organisms (Blunt et al., 2015). Out of these, 9 are approved as medical drugs and 13 are undergoing clinical trials (Gerwick and Moore, 2012; Rangel and Falkenberg, 2015). As examples from fungi, the diketopiperazine halimide (or phenylahistin) obtained from the marine fungi *Aspergillus ustus,* and its synthetic analog Plinabulin (NPI 2358), are in Phase 3 clinical trial for the treatment of non-small cell lung cancer (Raphael et al., 2017) and Phase 2 clinical trial for Neutropenia prevention (Nalley, 2017).

2. Cosmetics-cosmeceuticals from marine sources

The word cosmeceutical was derived from a blending of the terms ‘cosmetic’ and ‘pharmaceutical’ by Abbert Kligman in 1984 (Draelos, 2005). Cosmeceuticals are topical or oral cosmetic, pharmaceutical hybrids, intended to enhance beauty through the application of a bioactive ingredient having drug like benefits (Dureja et al., 2005; Kim, 2011). Therefore, cosmetics have been placed between non-prescribed and prescribed products in a regulatory sense (Amer and Maged, 2009). Cosmetics are defined as substances intended to be applied to the human body for cleaning, beautifying and promoting attractiveness, without affecting the bodies structure and function. Skin is the largest organ in our body and it plays an important role in protecting our body from external environmental stress and pathogens (Slominski et al., 2008). However a range of lifestyle and environmental factors cause cosmetics and dermatology problems (Kim, 2011). Skin cosmeceuticals were developed after research on common skin problems like hyperpigmentation, skin cancer, skin microbial infections, wound healing, and wrinkles associated with sun damage and ageing (Fig. 1). It has been reported that the global cosmeceuticals market will reach US$ 430 Billion by 2020 (https://www.alliedmarketresearch.com).

Natural cosmeceutical products that are safe and efficacious are

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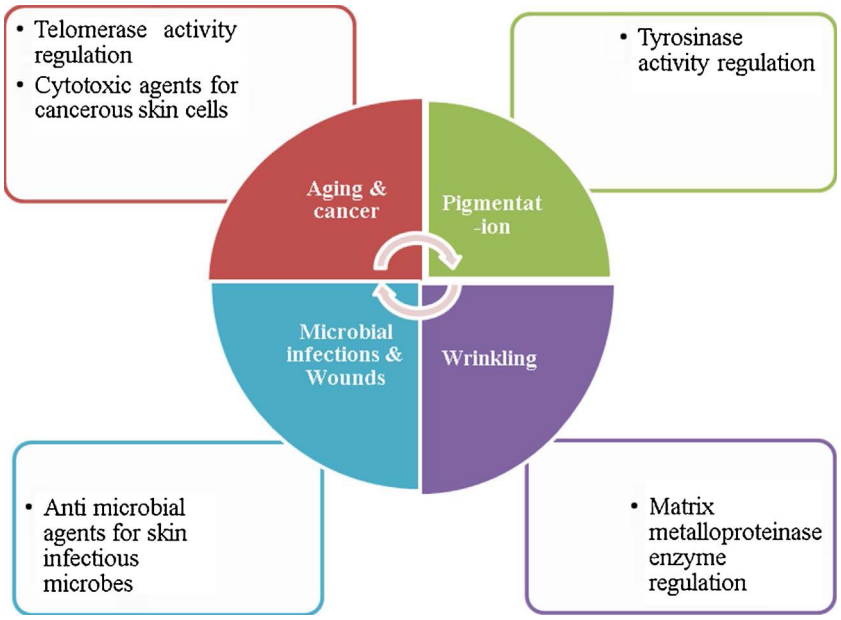

Fig. 1. Major worldwide skin problems and their probable solutions.

important for overcoming skin health problems. Plant derived ingredients have some limitations because plants generally grow too slowly and their chemical composition varies from season to season (Chermahini et al., 2011). However, marine flora and fauna produce chemically different biomolecules in comparison to terrestrial sources and so are of interest, particularly where organisms can be grown rapidly and cost effectively in large quantities, such as for macroalgae and microalgae. Examples include the Greek company Apivita that is using sea fennel in sun care products, whilst Italy-based Lacote has a comprehensive range of anti-cellulite skin care products formulated with Guam seaweed. Sea algae, rich in vitamins and minerals, is becoming a prolific source of anti-ageing bioactives.

The popularity of marine ingredients is leading to concerns that large-scale sourcing, or non-sustainable production methods, could disrupt marine ecosystems already under strain. Cultivable marine microorganisms can be grown outside the ocean in fermenters and so are sustainable. Many classes of bioactive molecules have been isolated from marine microbes for cosmeceutical applications, including phlorotannins, polysaccharides, carotenoid pigments, collagen, chitooligosaccharide (COS) derivatives, enzymes, peptides and other natural materials (Corinaldesi et al., 2017; Kim, 2011).

The potential of secondary metabolites from marine fungi as cosmeceutical ingredients has only being partially evaluated. Relative to the available biological and chemical diversity, only a few compounds have been isolated and utilized as cosmetic ingredient from marine fungi (Corinaldesi et al., 2017). Therefore, there is considerable potential in screening marine fungal isolates and their secondary metabolites for cosmeceutical activity. In the following sections we summarize research performed over the last 10 years on marine fungal natural products with cosmeceuticals activities.

3. Marine fungi and secondary metabolites

Marine fungi are an ecologically rather than physiologically or taxonomically defined group of microorganisms. Marine fungi are divided into two groups on the basis of their ability to grow in marine conditions, these being obligate and facultative marine fungi (Borse et al., 2012). Obligate marine fungi grow fast and sporulate exclusively in a marine or estuarine habitat, while facultative marine fungi have generally developed in terrestrial environments and adapted to the marine environment. Marine fungi are found to be associated with algae, corals, and detritus of marine macrophytes. Over 1500 species of marine fungi, including about 530 species of obligate marine fungi are known. Sometimes it is difficult to differentiate the obligate or facultative nature of fungi and therefore, a more general expression "marine-derived fungi" is used (Bugni and Ireland, 2004).

Marine fungi are major decomposers of woody and herbaceous substrates in marine ecosystems, and they also degrade dead animal or their parts (Hyde et al., 1998). Moreover, marine fungi are important pathogens of marine plants and animals and also form symbiotic relationships with other organisms (Hyde et al., 1998). A broad variety of substrates are available in marine and estuarine environments for fungal growth. These include seaweeds, decaying leaves, mangroves, dead animals, algae, shells of various mollusks (Rateb and Ebel, 2011). Most of these fungi grow on lignocellulosic material in the coastal as well as deep sea environments (Jones et al., 2009). To date 3047 species of fungi have been reported from aquatic habitats around the world. Worldwide, nearly 100000 fungal species are known and about 27500 species have been reported in India. The higher filamentous marine fungi include 530 species in 321 genera, which includes Ascomycota (424 sp. 251 genera), Mitosporic fungi (94 sp. 61 genera) and Basidiomycota (12 sp. 9 genera) (Jones, 2011a, 2011b).

Extreme physical and chemical conditions in the marine environment contribute to the production of a diverse chemical scaffolds by marine organisms (Kijjoa and Sawangwong, 2004). Some marine fungi have developed specific metabolic pathways which are not seen in terrestrial fungi (Abdel-Lateff, 2008; Liberra and Lindequist, 1995). Marine mangroves and algicolous fungi are significant sources of new bioactive compounds (Bugni and Ireland, 2004). Coral reefs are also a rich source of marine fungi that produce novel secondary metabolites due to the presence of other biotic components present in the reefs (Thomas et al., 2010). It is impossible to estimate how many marine derived fungi have been screened so far for bioactive compounds. However, it is clear that the number of new bioactive compounds reported from marine fungi has increased steadily over the years (Duarte et al., 2012; Rateb and Ebel, 2011; Saleem et al., 2007).

Some marine fungi have provided promising new lead structures for drug discovery (Murphy et al., 2012; Waters et al., 2010). An important example is the discovery of cephalosporin C (a non-ribosomal peptide secondary metabolite) from a marine fungi *Cephalosporium* sp. (Rateb and Ebel, 2011). Over the past decade, more than 10,000 marine natural products have been isolated from marine organisms, including marine fungi (Blunt et al., 2015; Kijjoa and Sawangwong, 2004). During this period, approximately 1000 new natural products have

been isolated from marine fungi, including terpenoids, alkaloids, shikimate-derived metabolites, lipids and most importantly polyketides and non-ribosomal peptides (NRPs) (Rateb and Ebel, 2011). These compounds have a broad array of pharmacological activities, ranging from antimicrobial to anti-cancerous activity (Rateb and Ebel, 2011), although only a few marine fungus based drug are currently in the market (Kiuru et al., 2014).

3.1. Marine fungi for the prevention of skin ageing

According to Euromonitor International, anti-ageing skin care is a large and dynamic industry, covering 22% of the global skin care market, worth US$ 66 billion in 2007 and is supposed to reach US$ 216 billion by 2021 (http://www.zionmarketresearch.com) (Bronaugh and Katz, 2010; Gasco-Buisson, 2010). In the United States 13% of the population were over the age of 65 in 2000 and this group is expected to increase to 20% by 2030 (Kosmadaki and Gilchrest, 2002). An ageing population suggested that there will be increasing efforts to preventing skin ageing and an increased demand for the development of safe and effective products related to ageing in general.

Ageing is a complex, multifactorial biological process that occurs in all living creatures at variable rates (Puizina-Ivic, 2008). Various surgical and topical remedies have been applied to alter the ageing process (Gorouhi and Maibach, 2009). There are two types of skin ageing processes, intrinsic and extrinsic, with skin ageing being the result of both processes affecting cell health and functioning (Baumann, 2007). Intrinsic or innate ageing refers to natural programmed cellular ageing. Cellular ageing is characterized by decreased collagen synthesis, degeneration of elastic fiber networks, and loss of hydration (Baumann, 2007). On the other hand, extrinsic ageing (premature cutaneous ageing) occurs as the result of external factors such as smoking, excessive alcohol consumption, poor nutrition, pollution, and particularly solar exposure. Solar exposure causes skin wrinkling and undesired pigmentation (Bosch et al., 2015). Extrinsic ageing, also known as photo ageing, has been studied extensively (Tsatsou et al., 2012). Skin ageing is governed by intrinsic genetic factors and mediated by extrinsic influences.

Marine organisms are a good source of photo-protective compounds. In particular, photosynthetic organisms have been investigated as sources photo-protective compounds, including mycosporines, mycosporine-like amino acids and several other UV filters, such as carotenoids and scytonemin (Pallela et al., 2010; Rastogi et al., 2010). Marine fungi *Phaeotheca triangularis*, *Trimmatostroma salinum*, *Hortaea werneckii*, *Aureobasidium pullulans* and *Cryptococcus liquefaciens* are known to produce mycosporine (mycosporine–glutaminol–glucoside and mycosporine–glutamicol–glucoside) (Kogej et al., 2006) and these molecules absorb UV in the range of 310–320 nm. Similarly, marine fungi belonging to the genera *Rhodotorula*, *Phaffia* and *Xanthophyllomyces* are a potential source of carotenoids (Vílchez et al., 2011). These carotenoids have significant anti-oxidant and anti-inflammatory effects that can contribute to skin photo-protection. Carotenoids can also inhibit adverse processes induced or mediated by solar UV radiation. However, marine fungi have not been examined as extensively as photosynthetic organisms, such as algae, for the production of carotenoids. A marine fungus of the genus *Exophiala* was the source of three novel benzodiazepine alkaloids, circumdatin I, C and G. These compounds showed high UVA screening activity with ED_{50} values of 98, 101 and 105 μM, and were more efficient than oxybenzone (ED_{50}, 350 μM), which is currently used in sunscreen (Zhang et al., 2008).

Oxidative changes are a principle causes of skin ageing. Topical and oral use of antioxidants has shown a preventative effect on skin ageing caused by free radicals or oxidative stress (Palmer and Kitchin, 2010). Marine fungi are an excellent source of anti-oxidant compounds (Rateb and Ebel, 2011). The marine fungus *Acremonium* sp., was found to produce four novel hydroquinone derivatives with significant anti-oxidant activity (Abdel-Lateff et al., 2002). Likewise, a macroalgae (*Fucus vesiculosus*) derived fungi *Epicoccum* sp. was found to produce an isobenzofuranone derivative (4,5,6-trihydroxy-7-methylphthalide) with a high α,α-diphenyl-picrylhydrazyl (DPPH) radical scavenging activity (Abdel-Lateff et al., 2003). Recently, *Aspergillus wentii* EN-48 isolated from brown algae was found to produce eight secondary metabolites with anti-oxidant activity (Li et al., 2014) that was considerably higher than that of the commonly used synthetic antioxidant butylated hydroxytoluene (Li et al., 2014). The anti-oxidant exopolysaccharide EPS2 was isolated from the marine filamentous fungus *Keissleriella* sp. YS 4108 and showed strong scavenging activity for superoxide radicals (Sun et al., 2004). Another marine *Aspergillus* sp was the source of the antioxidant diketopiperazine alkaloid golmaenone and a related alkaloid, as well as dihydroxy isoechinulin A and echinulin (Li et al., 2004a, 2004b). Golmaenone and the related alkaloid exhibited significant radical scavenging activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH), with an IC_{50} of 20 M, which is similar to that of ascorbic acid (IC_{50}, 20 M)(Li et al., 2004b). Furthermore, these compounds also displayed UV-A screening activity, with ED_{50} values of 90 and 170 M, and so were more efficient than oxybenzone (ED_{50}, 350 M)(Li et al., 2004b). These studies indicate the potential of marine fungi as sources of cosmeceuticals.

3.2. Marine fungi for skin whitening

Human skin color ranges from the darkest brown to the lightest pinkish-white due to varying melanin levels in the skin. Melanin is the major skin pigment that protects skin from harmful UV radiation. Longer exposure to ultraviolet (UV) radiation increases skin melanogenesis and usually results in darkening of the skin (Costin and Hearing, 2007). However, it may also occasionally lead to the development of hyperpigmentation. The biosynthetic pathway for melanin formation was first elucidated by Raper in 1928 and later modified by Cooksey in 1997.

Tyrosinase (EC 1.14.18.1), a copper-containing glycoprotein, is located in the membrane of the melanosome and produced only by melanocytic cells (Jeon et al., 2005). Melanogenesis takes place in the melanosomes and involves three enzymes. These are tyrosinase, tyrosinase-related protein (Trp)-1, and Trp-2. There are two types of melanin, which are synthesized within melanosomes; eumelanin (a dark brown-black insoluble polymer) and pheomelanin (light red-yellow sulphur-containing polymer). The amino acid L-tyrosine acts as a substrate for the enzyme and is generally transported into the melanosome by facilitated diffusion. The two proteins Trp-1 and Trp-2 are structurally related to tyrosinase and share approximately 40% amino acid homology. Trp-1 increases the ratio of eumelanin to pheomelanin and hence increases tyrosinase stability (Abu Ubeid and M Hantash, 2014; Lee et al., 2012). Tyrosinase catalyses the first two steps of melanin synthesis. Firstly, hydroxylation of L-tyrosine to dopaquinone that is subsequently converted into L-dihydroxyphenylalanine (L-DOPA) through auto-oxidation. Secondly, L-DOPA is converted to dopaquinone (Fais et al., 2009; Solano et al., 2006). The remaining steps of the melanogenic pathway, which include the synthesis of eumelanin and pheomelanin, are described by Chang (Chang, 2009).

Tyrosinase inhibitors have been proposed to be clinically useful for the treatment of some dermatological diseases associated with melanin synthesis like hyperpigmentation, melasma, caféaulait spot and solar lentigo. They are also useful in cosmetic applications such as skin lightening (Reszko et al., 2009). There are a large number of *in vitro* active tyrosinase inhibitors that have been reported from natural sources, but only a few have been found effective in clinical trials. (Chang, 2009; Wu, 2014). Table 1 and Fig. 2 describe *in vitro* tyrosinase inhibitors from marine fungi. Two new 3-amino-5-ethenylcyclopentenones, myrothenones A and B, have been isolated from fungus of the genus of Myrothecium. Only myrothenones A exhibited tyrosinase inhibitory activity, with an IC_{50} value of 0.8 uM (Li et al., 2005). This compound is more active than kojic acid (IC_{50} value 7.7 uM), which is

Table 1
Tyrosinase inhibitors from marine fungi.

Sr. No.	Biomolecule	Source	Habitat	References
1.	Myrothenones A and B (Cyclopentenone)	*Myrothecium* sp.	Green algae *Entemorpha compressa*	Li et al., (2005)
2.	6-[(*E*)-Hept-1-enyl]-α-pyrone (α-Pyrone Derivative)	*Botrytis* sp.	Marine red alga *Hyalosiphonia caespitose*	Zhang et al. (2007)
3.	Homothallin-II	*T. viride* H1-7	Marine sediments	Tsuchiya et al. (2008)
4.	1β,5α,6α,14-tetraacetoxy-9α-benzoyloxy-7β H-eudesman-2β 11-diol and 4α,5α-diacetoxy-9α-benzoyloxy-7βH-eudesman-1β,2β,11, 14-tetraol	*Pestalotiopsis* sp. Z233	Algae *Sargassum horneri*	Wu et al. (2013)

currently used in various skin whitening products. A new α-Pyrone derivative, 6-[(E)-Hept-1-enyl]-α-pyrone, was isolated from the marine fungus *Botrytis* sp. This compound exhibited greater tyrosinase inhibitory activity than kojic acid (IC_{50} value 4.5 versus 15.5 μM, respectively) (Zhang et al., 2007). Homothallin II, a competitive inhibitor against the mushroom tyrosinase, was isolated from marine derived *Trichderma viride.* This compound inhibits the enzyme through binding to a copper active site of the mushroom tyrosinase (Tsuchiya et al., 2008). Two new sesquiterpenes, 1β, 5α, 6α, 14-tetraacetoxy-9α-benzoyloxy-7β H-eudesman-2β, 11-diol and 4α, 5α-diacetoxy-9α-benzoyloxy-7βH-eudesman-1β, 2β, 11, 14-tetraol, were isolated from *Pestalotiopsis* sp. Z233 obtained from the algae *Sargassum horneri.* These compounds showed tyrosinase inhibitory activities with IC_{50} value of 14.8 μM and 22.3 μM, respectively (Wu et al., 2013).

3.3. Marine fungi for acne vulgaris as antibacterial

Acne vulgaris (commonly known as acne or pimples) is the most common skin disorder and is caused by *Propionibacterium acnes* (Coates et al., 2002). *Staphylococcus epidermidis* is also isolated from acne lesions (Nishijima et al., 2000). This disoreder affects approximately 50 million people in the US, and many more throughout the world (Tan and Bhate, 2015). Globally, more than 80% of the populations suffer from acne at some stage in their life. Acne can be extremely painful and cause lasting marks or scars as well as lead to psychological suffering. Economically, it is estimated that US consumers spend more than 1.2 billion dollars each year for the treatment of acne (Lee et al., 2003).

An investigation into the prevalence of skin colonization by antibiotic-resistant *Propionibacterium acnes* in acne patients over a 10-year period (Coates et al., 2002) showed that the proportion of patients with strains resistant to one or more commonly used anti-acne antibiotics is increasing (Sardana et al., 2015; Walsh et al., 2016). In people with acne, 18·8% of *P. acnes* strains and 51·7% of *S. epidermidis* strains were resistant to clindamycin. Over 80% of individuals who had clindamycin-resistant *P. acnes* also had clindamycin-resistant *S. epidermidis* (Walsh et al., 2016). Therefore there is a need to discover new bioactive molecules against both *P. acnes* and *S. epidermidis*. Recently, two unusual pyridones, trichodin A and trichodin B (Fig. 3**)**, were extracted from mycelia and culture broth of the marine fungus, *Trichoderma* sp. strain MF106 isolated from the Greenland Seas. Trichodin A and B showed antibiotic activity against *S. epidermidis*, with IC_{50} values of 24 μM and 4 μM, respectively (Wu et al., 2014).

4. Conclusions and future prospects

Marine research has the potential to discover new marine-based compounds for cosmeceutical applications. The large microbial diversity of the marine environment remains only partially explored. Marine fungi are rich-sources of structurally diverse and biologically active metabolites, with industrial potential. Thus, they have attracted attention for health and cosmetic applications (Corinaldesi et al., 2017). In this review, we have summarized work done on marine fungal secondary metabolites with regard to skin ageing, depigmentation and anti-acne applications relevant to the cosmetic industry. However, the

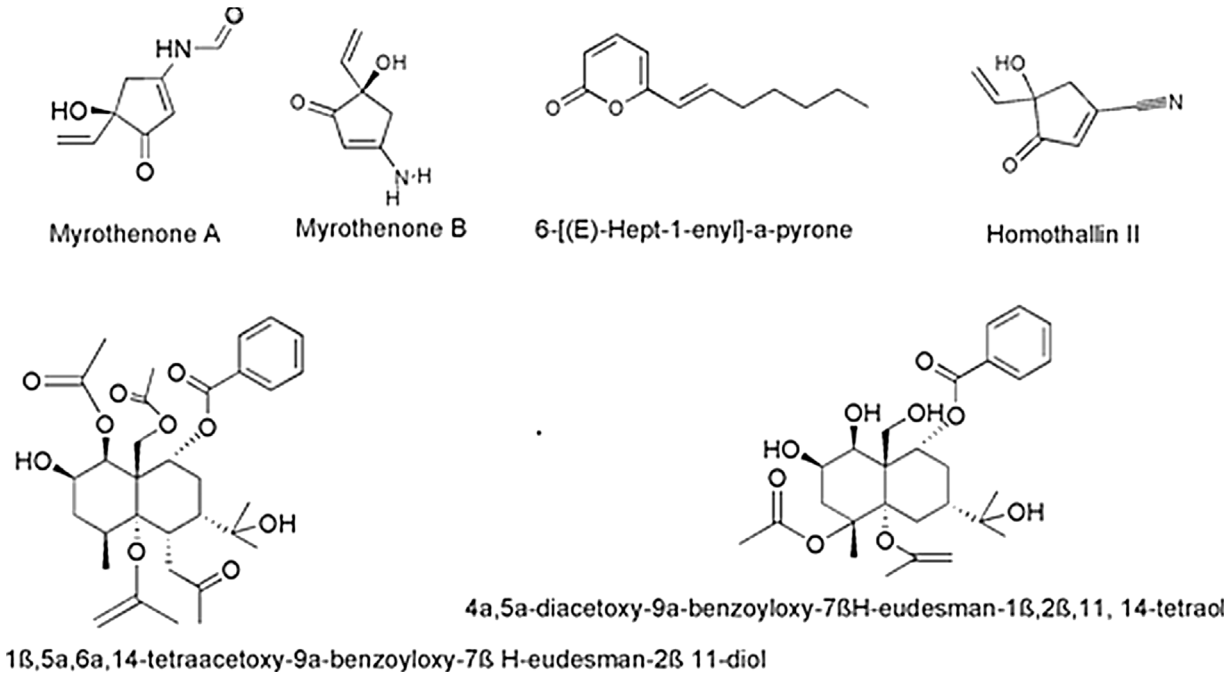

Fig. 2. Tyrosinase inhibitors from marine fungi.

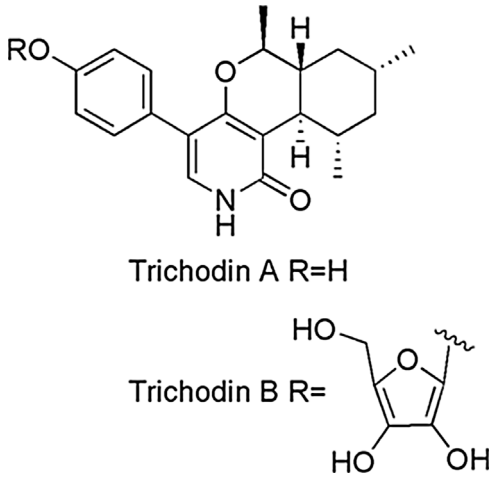

Fig. 3. Structure of Trichodin A-B.

use of fungal secondary metabolites, in particular from the marine envronment, remains relatively unexplored for cosmetic applications. To increase success in identifying new secondary metabolites from marine fungi for cosmeceuticals, improvements in our understanding fungal physiology and more efficient methods for metabolite production are needed.

The production of secondary metabolites is highly dependent on the culture conditions and the origin of the strains (Kossuga et al., 2012). Secondary metabolites are synthesized mainly under stress conditions due to either nutrition limitation or excess of carbon sources. The five main sources for the synthesis of secondary metabolites are (1) amino acids, (2) shikimic acid pathway, (3) polyketide biosynthesis pathway from acetyl CoA, (4) mevalonic acid pathway from acetyl CoA (5) polysaccharides and peptidopolysaccharides. The production of secondary metabolites by marine fungi varies due to several factors such as media composition, salt concentration and other fermentation parameters. The effect of sea water concentration on hyphal growth and anti-microbial metabolite production was studied in various marine fungal strains and was found to increase hyphal as well as metabolite production with increased sea water concentration (Huang et al., 2011; Masuma et al., 2001). The antibiotic lipoxazolidinones was produced by the marine fungal strain NPS8920 and its levels increased in natural sea water based media (Sunga et al., 2008). Miao et al. (2006), illustrating the impact of salinity and nutrition on the growth and bioactivity of marine fungi. This study concluded that higher salt concentration decreased fungal growth, but increased bioactivity. Also, higher concentrations of peptone and malt extract in growth media enhances fungal growth but decreases antibacterial activity, whereas the opposite occurred at higher glucose concentrations. For instance Wang et al. (2011), studied secondary metabolite production in the marine fungi *Spicaria elegans* at 3% and 10% salinity. Five new compounds were produced at 10% salinity, which were absent at 3% salinity. Therefore, regulation of physico-chemical conditions were important for optimizing secondary metabolite production in marine fungi in this instance, and probably more generally.

While advances from genome sequencing and tool development (e.g., RNAi, CRISPER) will undoubtedly be valuable, the use of culture-independent strategies and “omics” approaches to study marine diversity may be critical for the advancement of marine fungi research and associated cosmetic applications (Owen et al., 2013). Most studies on marine fungi have so far dealt with only easily cultivable fungi, leaving behind slow growing and unculturable marine fungi. Methods to culture these species such as simulated natural environments for culturing deserve a closer look. The use of epigenetic tool like histone and DNA modification can be used to modulate the biosynthetic pathway for the production of secondary metabolites of fungi.

The co-culture strategy for obtaining chemically different compounds is promising since microorganisms live in extremely biodiverse communities in their natural habitat. Co-culture generates a complex and promising environment to obtain new secondary metabolites. As a response to the interaction between marine microbes, co-culture conditions can amplify metabolic mechanisms and trigger production. It is also important to screen previously isolated natural products from marine fungi for new bioactivity, including for cosmeceutical applications.

Some limitations exist in exploring the full diversity of marine fungi, such as restrictive access to remote and deep water locations for sample collection. However many areas are easily accessible, such as shallow water ecosystem, although deep seas that are relatively unexplored represent 95% of available area. Therefore, the ocean still has enormous potential for the discovery and development of new and bioactive compounds of fungal origin for technological and cosmeceutical purposes (Corinaldesi, 2015), and methods to access remote and deep locations will be important in future biodiversity exploration.

Ethics approval and consent to participate

Not applicable.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author contributions

SA collected the relevant information from various sources including databases like Scifider and wrote the paper. AA gave the concept of the work. SD reviewed the collected information critically. CB reviewed the work and contributed to writing the paper.

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