

# **Biotechnological Application** of Extremophilic Fungi

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#### Abstract

White biotechnology (BT), a sustainable and eco-friendly technology, has taken precedence over chemical industries in the last few decades. It has revolutionized the industrial BT sector by exploiting abundant natural resources for the production of important commodities benefiting mankind. Industries employ microorganisms or biomolecules extracted from them for production and processing in various industrial areas such as food and feed, beverages, agriculture, pharmaceutical, textile, leather, paper, detergent, polymers, cosmetics, waste management, etc. Despite the advantages, the use of biomolecules is not substantial because they cannot tolerate harsh industrial conditions, which in turn affects the production process. In the last decade, the industrial research focus has shifted toward extremophiles, organisms that can survive extreme conditions. These organisms have evolved defense mechanisms to survive severe conditions such as high or low temperature, salinity, pressure, pH, radiation, and desiccation. Biomolecules extracted from these organisms have robust characteristics to retain optimum activity even under unnatural conditions. A class of eukaryotes called extremophilic fungi are at the crux of this research focus as they are a reservoir of sturdy biomolecules with many industrial applications. Fungal extremozymes can be easily cultured on agro-industrial waste and also easily purified. All these factors make fungal extremozymes an attractive resource for large-scale, costeffective, and eco-friendly industrial processes. In addition to extremozymes, extremophilic fungi are an abundant resource of potent cytotoxic, antimicrobial

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S. Sahay (ed.), Extremophilic Fungi, https://doi.org/10.1007/978-981-16-4907-3\_15

drugs. This chapter focuses on various extremophilic fungi used in the BT industry. It also covers the different extremozymes, biomolecules, and secondary metabolites secreted by them and their potential biotechnological applications.

#### Keywords

# 15.1 Introduction

A sustainable bio-based economy is a ray of hope in response to the present environmental crisis such as population expansion, climatic changes, exhaustion of nonrenewable resources, global warming, pollution, etc. The advent of bioprocess technology, also known as white biotechnology, has revolutionized the industrial sector by exploiting natural resources for the production and processing of valueadded products that positively impact the global economy and environment. This contemporary technology employs enzymes or microorganisms such as yeast, bacteria, fungi, and plant extracts in numerous industrial applications. Fungal sources have been the major contributors in this field as many enzymes, organic acids, antibiotics, etc., are produced on a commercial scale (Meyer et al. 2016). The discovery of penicillin, fungal antibiotics along with the commercial production of citric acid by Aspergillus niger, marked a milestone in the era of fungal biotechnology, and since then many more discoveries have steadily transformed it into a powerful and proficient technology. Fungi play a vital and irreplaceable role in energy recycling of the ecosystem by helping in the decomposition and recycling of organic matter. This versatile class of eukaryotes are omnipresent and can be found in soil, desserts, glaciers, sea, freshwater bodies, and various other environments including the stratosphere (van der Giezen 2011). Fungi have proven to be a valuable resource to humanity from being consumed as food to combating infectious diseases and many biomolecules with important industrial applications. Besides, helping in the fermentation processes of baking, brewing, etc., they aid in the production of enzymes, antibiotics, organic acids, pigments, vitamins, lipids, and numerous other products that are economically important (Adrio and Demain 2003). Their fast growth rate, short life cycles, ease of culture, and purification are highly favorable attributes that benefit the industrial production processes (Hooker et al. 2019).

Fungi are highly resilient organisms that can adapt to diverse habitats and due to their ecological plasticity, they can survive harsh environments precluded to most life forms. They dwell in virtually all types of extreme habitats ranging from extremely dry and cold deserts in the Antarctic and other very cold areas worldwide to highest mountain peaks (Selbmann et al. 2008) to deep permafrost soils (Ozerskaya et al. 2009; Selbmann et al. 2015), geothermal and fumarole soils in volcanic areas, acid mine drainages with sulfuric acid (Selbmann et al. 2008), or in highly alkaline sites (Gunde-Cimerman et al. 2009; Selbmann et al. 2013). Under

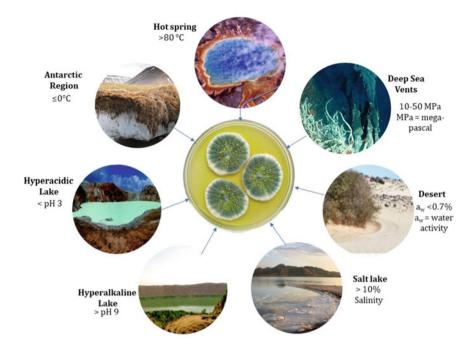


Fig. 15.1 Extreme environments of the earth

severe conditions and high competition, fungi acquire peculiar skills to exploit natural or xenobiotic resources and such fungi are termed as extremophilic fungi (Zhang et al. 2018).

These fungi have evolved defense mechanisms in the form of regulation and expression of specific genes or production of robust enzymes that help them to survive conditions such as high or low temperature, salinity, pressure, pH, radiation, and desiccation. Biomolecules extracted from these organisms have robust characteristics and retain optimum activity even under harsh industrial conditions. All these factors make fungal extremozymes an attractive resource for large-scale, cost-effective, and eco-friendly industrial processes, and the scope to use extremophilic fungi for biotechnological applications is increasing with time (Sarmiento et al. 2015).

The term "extremophile" was first proposed by MacElroy in 1974 to describe a broad group of organisms that can live optimally under extreme conditions. They belong to all three domains of life —Eucarya, Bacteria, and Archaea. Extremophiles are classified into seven categories based on the extreme habitats they inhabit (Fig. 15.1). Piezophiles can survive high hydrostatic pressure and have been isolated from deep sea sediments (>3000 m deep). Thermophiles or hyperthermophiles are organisms that inhabit hot springs, deep sea hydrothermal vents, and can tolerate very high temperatures varying from 50 to 80 °C or over 80 °C (Raddadi 2015). Some halotolerant fungi can tolerate high salt concentration and abiotic stress

(Gunde-Cimerman et al. 2003). This is why many fungi inhabit marine environments. Alkalophiles can tolerate a pH range between 9 and 12, whereas acidophiles can survive extremely low pH of 1–2 (Jin and Kirk 2018). Psychrophiles are the next class that can tolerate extreme cold conditions of the Antarctic zone (Selbmann et al. 2008) and some yeasts can survive ultraviolet rays (UV-B) exposure even at lethal doses (Selbmann et al. 2011). Due to their uncommon adaptability, fungi may also easily colonize stressful and extreme environments created by anthropogenic activities, such as those polluted with heavy metals, toxic chemicals, sewage, etc. (Ceci et al. 2019). Therefore, polluted sites are a rich source to screen for extremophilic fungi. Fungal strains isolated from these environments are strongly adapted to high toxicity and extreme physical parameters (i.e., high salt concentration and high pH). These strains are potentially useful in biotechnological applications such as the biodegradation of the pollutants (Gomes and Steiner 2004: Selbmann et al. 2013) or they can be considered as sources of important bioactive compounds, specific enzymes, biosurfactants, and antioxidants, useful for applications in medicine or food, cosmetics, and chemical industry (Adrio and Demain 2003). They are also employed in biofuel and bioenergy industries since solar cells of specialized pigments work only under extreme conditions like polar caps.

## 15.2 Biotechnological Applications

Biotechnological industries are exploiting a variety of enzymes as solutions to numerous industrial processes. Fungi from the extreme environment are considered a vital source of commercial hydrolytic enzymes due to their exceptional properties of high catalytic activity, stability, high enzyme yield, ease of culture, and retention of activity even under high-stress conditions. Lipases, amylases, proteases, cellulases, xylanases, etc., are highly used in industries that require efficient breakdown of lignocellulosic biomass in the processing and production of good quality biobased products. Hence, fungal extremozymes help in large-scale, cost-effective, and eco-friendly industrial processes that could significantly affect the growth of the biotechnology sector (Shukla and Singh 2020). Some of the important fungal extremozymes are listed in Table 15.1. The important fields that use these enzymes include decolorization of dyes in the textile industry, detoxify pesticides, degrade agricultural waste to valuable by-products, delignify biomass for biofuel production, bleach the kraft pulp in the paper industry, processing and stabilization of juice, wine, bakery products in the food industry, bioremediation, and many other processes (Baldrian 2006; Brijwani et al. 2010). Along with extremozymes, secondary metabolites and bioactive peptides are also products of extremophilic fungi. Their potential role in preventive medicine as antimicrobials, antivirals, cytotoxic agents, antitumorigenic, antidiabetic, anti-inflammatory, lipid-lowering activities is also illustrated in this chapter (Fig. 15.2).

Enzymes	Organisms	Applications in industries	References
Proteases	Penicillium buponti, Malbranchea pulchella var. sulfurea, Humicola lanuginose Rhodotorula mucilaginosa L7 Leucosporidium antarcticum Acremonium sp. L1–4B Pseudogymnoascus pannorum Candida humicola	Food, detergents, leather, pharmaceutical, agricultural industries	(Maheshwari et al. 2000) (Lario et al. 2015) (Turkiewicz et al. 2003) (Evaristo da Silva Nascimento et al. 2015) (Krishnan et al. 2011) (Ray et al. 1992)
Laccases	Chaetomium thermophilium Corynascus thermophiles aspergillus oryzae Aigialus grandis, Cirrenalia pygmea, Gliocladium sp., Hypoxylon oceanicum, Halosarpheia ratnagiriensis, Gongronella sp., Sordaria fimicola, Verruculina enalia and Zalerion varium. Cladosporium halotolerans, Cladosporium sphaerospermum, Penicillium canescens. Cerrena unicolor (MTCC 5159) and Penicillium pinophilum (MCC 1049)	Paper and pulp, Textile industry, agriculture, Food and beverages	(Chefetz et al. 1998) (Babot et al. 2011; Berka et al. 1997; Bulter et al. 2003; Xu et al. 1996) (Raghukumar et al. 1994) (Jaouani et al. 2014) (D'Souza-Ticlo et al. 2009)
Cellulases	Trichoderma resei Chaetomiumthermophile, Sporotrichum thermophile, Humicola grisea var thermoidea, Humicola insolens, Myceliopthera thermophila, Thermoascus aurantiacus and Talaromyces emrsonii Cadophora, Pseudeurotium, Geomyces, Wardomyces, Pseudogymnoascus,	Biofuel production, paper and pulp, Textile	(Mandels and Weber 1969 (Maheshwari et al. 2000) (Krishnan et al. 2011; Tsuj et al. 2014; Vaz et al. 2011 Wang et al. 2013)

 Table 15.1
 Extremophilic enzymes sources and uses in industries

(continued)

Enzymes	Organisms	Applications in industries	References
	Verticillium, Cryptococcus and Mrakia		
Xylanases	Aureobasidium pullulans varmelangium, Pencillium occitanis PO16, Aureobasidium pullulans Pencillium oxalicum Pencillium citrinum, Aspergillus fumigatus Humicola insolensY1, Sporotrichum thermophile Rhizomucor pusillus, Aspergillus gracilis, Aspergillus penicillioides Naganishia adeliensis.	Paper and pulp, Animal feed, Textile, Food and brewery	(Ohta et al. 2001) (Driss et al. 2011) (Yegin 2017) (Muthezhilan et al. 2007) (Dutta et al. 2007) (Deshmukh et al. 2016) (Du et al. 2013) (Sadaf and Khare 2014) (Robledo et al. 2016) (Ali et al. 2012) (Gomes et al. 2003)
Lipases	Rhizomucor miehei Kurtzmanomyces sp. I-11 Moesziomyces antarcticus Leucosporidium scottii L117 Mrakia blollopis SK-4 Geomyces sp. P7	Biofuel, detergent, food, and beverages	(Maheshwari et al. 2000) (Kakugawa et al. 2002; Goto et al. 1969) (Goto et al. 1969) (Duarte et al. 2015) (Tsuji et al. 2013) (Tsuji et al. 2013)
Amylases	Rhizomucor pusillus, Humicola lanuginose, Myriococcum thermophilum, Thermomyces ibadanensis, Thermomyces lanuginosus Candida antarctica Geomyces pannorum	Starch processing, food and beverage, paper and pulp, Textile, and pharmaceutical	(Adams 1994; Arnesen et al. 1998; Barnett and Fergus 1971; Bunni et al. 1989; Fergus 1969; Jayachandran and Ramabadran 1970; Sadhukhan et al. 1992) (Mot and Verachtert 1987) (Gao et al. 2016)
Pectinases	Aspergillus Niger Cryptococcus albidus var. albidus, Aspergillus Niger MTCC478, Saccharomyces cerevisiae, Penicillium sp. CGMCC 1669 Rhizomucor pusilis Thermomucor indicae- seudaticae Arthrobotrys, Aureobasidium, Cladosporium, Leucosporidium Tetracladium	Biofuel production, oil extraction, paper and pulp, food, and beverage	(Lara-Márquez et al. 2011) (Federici 1985) (Anand et al. 2017) (Gainvors et al. 2000) (Yuan et al. 2011) (Siddiqui et al. 2012) (Martin et al. 2010) (Fenice et al. 1997) (Carrasco et al. 2016)

Table 15.1 (continued)

(continued)

		Applications in	
Enzymes	Organisms	industries	References
Chitinases	Trichoderma, Oenicillium, Penicillium, Lecanicillium, Neurospora, Mucor, Beauveria, Lycoperdon, aspergillus, Myrothecium, Conidiobolus, Metharhizium, Stachybotrys, Agaricus Talaromyces emersonii, Thermomyces lanuginosus Dioszegia, Glaciozyma, Lecanicillium, Leuconeurospora, Mrakia, Metschnikowia Phoma, Sporidiobolus, Verticillium lecanii Glaciozyma antarctica PI12	Pharmaceutical and agricultural industry	(Hamid et al. 2013; Karthil et al. 2014) (McCormack et al. 1991) (Zhang et al. 2012) (Barghini et al. 2013; Carrasco et al. 2012; Fenico et al. 2012, 1998, 1997; Onofri et al. 2000) (Ramli et al. 2011)
Phytases	Aspergillus Niger Myceliophthora thermophila, Talaromyces Papiliotrema laurentii AL27 Rhodotorula mucilaginosa strain JMUY1	Bread making and animal feed	(Haros et al. 2001) (Maheshwari et al. 2000) (Pavlova et al. 2008) (Yu et al. 2015)

Table 15.1	(continued)
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## 15.2.1 Food and Beverage Industry

Use of enzymes instead of chemicals improves the quality of the processed food and creates superior products with improved yields. In addition, enzymes also play key role in enhancing the nutrition and appeal of the products. Enzymes are used in baking, making sugar syrups, cheese and dairy making, extraction and clarification of juices, oil, as sweeteners, for flavor development, meat tenderizing, etc., and in many other processes. From making food products to storage of food and beverage all require extreme conditions making extremozymes an essential ingredient to achieve food quality at low costs in this industry.

Cold-active enzymes produced by psychrophiles are flexible, resulting in higher catalytic activity at low temperatures (Arora and Panosyan 2019). These enzymes can be used to soften frozen meat products, preserve the heat-sensitive nutrients, accelerate cheese ripening, and they are also effective against wine and juice clarification. *Rhodotorula mucilaginosa* L7 is a yeast strain from the Antarctic region that produces acid protease with an activity range between 15 °C and 60 °C and pH 5 (Lario et al. 2015). A similar discovery of a psychrophilic and halotolerant serine protease from Antarctic region resulted in isolation of *Leucosporidium antarcticum* fungal strain where the enzyme was found most active at 10–25 °C

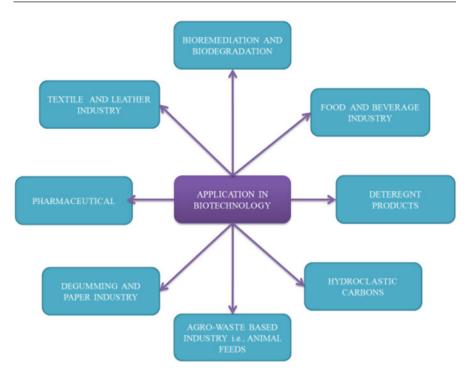


Fig. 15.2 Representation of extremophilic fungi biotechnological applications

and 3.5% marine salt (Turkiewicz et al. 2003). Additionally, Laccases have many applications like processing and stabilization of juice, wine, bakery products in the food industry, and many other processes (Baldrian 2006; Brijwani et al. 2010).

Amylases are another class of enzymes highly used in food industry; they are also used in various other industries such as starch processing, textile, food and beverage, paper, pharmaceutical, and many other industries (Pandey et al. 2000). Extremophilic fungal  $\alpha$ -amylases have achieved an important place in industrial enzymes. Many thermophilic fungal species studied so far are capable of secreting amylases. Rhizomucor pusillus, and Humicola lanuginose, Myriococcum thermophilum, Thermomyces ibadanensis, and Thermomyces lanuginosus are a few of the thermophilic fungi found to produce amylase enzyme (Sadhukhan et al.1992; Jayachandran and Ramabadran 1970; Fergus 1969; Bunni et al. 1989; Barnett and Fergus 1971; Arnesen et al. 1998; Adams 1981; Adams 1994). Psychotolerant fungi are also a good source of amylases. Candida antarctica from Antarctic region was observed to produce both  $\alpha$  and  $\gamma$  amylases. Both enzymes were active on high molecular weight polysaccharides with  $\alpha$ -amylase showing activity even on cyclodextrins (Mot and Verachtert 1987). Extremophilic fungal xylanases and pectinases also have many benefits such as pulping, juice and wine clarification, oil extraction etc. (Soni et al. 2017). Trichoderma sp, Aspergillus sp, Penicillium sp, and Acido bacterium spp. are the major extremophilic fungal genera

that contribute to the production of xylanases. Similarly, many acidic fungal pectinases like Aspergillus niger between pH 3 and 5.5 (Lara-Márquez et al. 2011). Cryptococcus albidus var. albidus, pH 3.75 (Federici 1985), Aspergillus niger MTCC478, pH 4 (Anand et al. 2016), Penicillium sp. CGMCC 1669, pH 3.5 (Yuan et al. 2011), and Saccharomyces cerevisiae pH 3–5.5 (Gainvors et al. 2000) have been screened. Novoshape (novozymes), pectinase 62 L (biocatalysts), and lallzyme (lallemand) are few commercially available foodbased companies that use pectinase enzyme (Dumorné et al. 2017; Sarmiento et al. 2015). Acidic pectinases are one such enzyme used in the clarification of fruit juices, beer, and wine as well (Kashyap et al. 2001). Recent research has indicatedS screening of bacterial strains known to produce alkaline and thermophilic pectinases. Anand et al. 2016 purified and characterized an alkaline pectinase from Aspergillus fumigatus MTCC 2584 having a pH optima of 10. In another study, thermophilic pectinase was purified from *Rhizomucor pusilis* having temperature optima of 55 °C was isolated (Siddiqui et al. 2012). Martin et al. 2010 also isolated a thermophilic pectinase producing fungal strain Thermomucor indicae-seudaticae that could grow at 45 °C. Recently, psychrophilic and pectinolytic fungi were isolated from Antarctic region. The representative genera are Arthrobotrys, Aureobasidium, Cladosporium, and *Leucosporidium* showed the pectinase activities even at 5 °C (Fenice et al. 1997). A cold-adapted pectinase-producing fungi was also isolated from Tetracladium sp. with highest activity at 15 °C (Carrasco et al. 2019).

### 15.2.2 Detergents

Extermophilic fungal lipases are sought-after enzymes in detergent industries as they possess robust properties. Particularly esterases (EC 3.1.1.1) and lipases (EC 3.1.1.3) are important as they catalyze the cleavage of esterbonds and also help in reverse reactions in organic solvents (Fuciños et al. 2012). Lipases help in acidolysis, alcoholysis, aminolysis, esterification hydrolysis, interesterification, etc. (Daiha et al. 2015), making them versatile and having many applications in organic and fine chemical synthesis, and cleaning products. A thermostable lipase from Humicola lanuginosa strain Y-38 was isolated from compost in Japan. The enzyme was thermophilic having temperature optima of 60 °C and alkalophilic with pH optima of 8.0. Rhizomucor miehei, formerly called Mucor miehei, also produced active lipase (Maheshwari et al. 2000). Kakugawa et al. (2002) reported a thermostable and acidophilic lipase-producing yeast strain Kurtzmanomyces sp. I-11 with optimum activity at 75 °C and pH 2–4. Another noteworthy example of thermostable and alkalophilic lipase is produced by *Thermomyces lanuginosus*, known as TLL showing maximum lipase activity between 60 and 85 °C and pH 10 (Avila-Cisneros et al. 2014). Lipolase, Lipoclean, and Lipex are few of the genetically improved lipases from the fungus Thermomyces lanuginosus included in detergent formulations by Novozymes (Jurado-Alameda et al. 2012). Cellulases are the next class of enzymes that have found applications in the detergent industry to increase brightness and dirt removal from cotton mixed garments (Kuhad et al. 2011). Many

commercially available detergents have been reported where enzyme such as lipase, protease, amylases, cellulases, and mannanases are included in the formulations (Sarmiento et al. 2015).

### 15.2.3 Paper and Pulp Industry

In the paper and pulp industry, the significant application of enzymes is in the prebleaching of kraft pulp. Xylanases, hemicellulases, and cellulases are the commonly used enzymes for this purpose due to its displayed efficiency. Enzymes have also been used to raise water retention, pulp fibrillation, and decrease the beating time in virgin pulps. Enzymes are also involved in increasing the freeness and in the deinking process (Dumorné et al. 2017; Bajpai 1999). Fungal laccases are involved in lignin degradation due to displayed efficiency (Alcalde 2007; Thurston 1994). Due to high enzyme yield and higher redox potential, fungal laccases are preferred over the plant or bacterial enzymes in the biotechnology sector (Thurston 1994). Corvnascus thermophilus is a fungal strain secreting highly active thermostable laccase that was used to delignify euclypt pulp. This laccase was heterologously expressed in Aspergillus oryzae, characterized, and commercialized (Xu et al. 1996; Berka et al. 1997; Bulter et al. 2003; Babot et al. 2011). Cellulases are also heavily used in this industry. Penicillium roqueforti, Cadophora malorum, Geomyces sp., and Mrakia blollopis are few of the cold-adapted cellulase-producing fungal strains (Carrasco et al. 2016; Duncan et al. 2006; Duncan et al. 2008). Trichoderma sp, Aspergillus sp, Penicillium sp, and Acidobacterium spp are the major extremophilic fungal genera that contribute to the production of xylanases.

# 15.2.4 Agricultural Applications

Many cellulolytic and xylanolytic fungi are acknowledged to have applications in the field of agriculture by boosting the seed germination, improved root system and flowering, increased crop yields, and rapid plant growth (Ahmed and Bibi 2018). Fungal xylanases such as *Pencillium oxalicum* (Muthezhilan et al. 2007), *Pencillium* citrinum (Dutta et al. 2007), Aspergillus fumigatus (Deshmukh et al. 2016), and Humicola insolensY1(Du et al. 2013) are isolated showing optimum activity between pH 8-9 and 45-55 °C with H.insolensY1 also being highly thermophilic with a temperature optima of 70–80 °C. Other thermophilic xylanase-producing fungi include Chaetomium sp. CQ31, Sporotrichum thermophile isolated from composting soil having activity at neutral pH and 60-70 °C temperature (Jiang et al. 2010; Sadaf and Khare 2014). Rhizomucor pusillus and Aspergillus fumigatus screened from the maize silage showed optimum xylanase activity at 75 °C and pH 6 (Robledo et al. 2016). Many thermophilic xylanase-producing fungi such as Chaetomium thermophilum, Humicola insolens, Melanocarpus sp., Malbranchea sp., and Thermoascus aurantiacus were reported by Ghatora et al. 2006. Halotolerant fungal xylanase *Phoma sp* isolated from mangrove sediments having enzyme activity at pH 5, 45 °C, and a high salt concentration of 4 M NaCl (Wu et al. 2018). Aspergillus gracilis and Aspergillus penicillioides were screened from man-made solar saltern (Ali et al. 2012) and psychrophilic fungal xylanases were isolated from Antarctic soils, marine sponges, etc. *Cladosporium sp.* from marine sponge showed high xylanase activity at low temperatures (Del Cid et al. 2014). *Naganishia adeliensis* are isolated from Antarctica (Gomes et al. 2003). Phytases are another class of enzymes involved in seed germination, but they are also considered antinutrients because they act as strong chelators of divalent mineral ions such as calcium, magnesium, iron, and zinc. Chitinases have many applications, especially as antiphytopathogenic and antifungal agents. They are used to protect crops to control pathogens. Cola-active extremozymes are used in agriculture to enhance the water management by plants, which are under deficiency stress (Dumorné et al. 2017).

#### 15.2.5 Animal Feed Industry

Cellulases and xylanases have advantage in the animal feed industry in the treatment of agricultural silage, grains, and seeds to enhance nutritional value. Cold-adapted phytases have advantages as they can be directly included in the feed of monogastric animals and also in aquaculture.

# 15.2.6 Bioremediation and Biodegradation: Major Application of Extremozymes

Bioremediation and biodegradation employ microbes in the elimination of pollutants, contaminants, and toxins from water, soil, and other environments. Waste from any kind of industry is hazardous. It is highly acidic or alkaline, and contains all kinds of biomass and proteinaceous waste. It also has a high content of metal ions and many other toxins, dyes, chemicals, radioactive material, etc., making it very harmful to the flora and fauna around it.

Certain microbes can be used to recycle and degrade pollutants as they produce hydrolytic enzymes that can degrade and help clean up the contaminated sites. Fungal extremozymes are extremely useful in these processes as they can sustain harsh conditions and still work on organic toxins. Thermophiles convert recalcitrant materials in bioprocessing and favor the in situ bioremediation process (Castro et al. 2019). As the solubility of the pollutants increases, the metabolic activity of thermophiles also increases (Zeldes et al. 2015). Thermophilic fungi such as *Pyrodictium, Clostridium,* and *Methanopyrus* can metabolize naphthalene, anthracene, and phenanthrene (Ghosal et al. 2016). White rot fungi are the chief representatives of the biodegradation of lignin substances (Deshmukh et al. 2016). 21 PAH degrading fungi were isolated from PAH-contaminated soils that could efficiently degrade PAH. Aspergillus niger, Diaporthe sp., Coriolopsis byrsina, *Pestalotiopsis sp.,* and *Cerrena* are known to treat and bioremediate textile mill

effluents (Rani et al. 2014). *Stenotrophomonas maltophilia* strain AJH1 has been isolated from Arabia, which was able to degrade low and high molecular weight PAHs such as anthracene, naphthalene, phenanthrene, pyrene, and benzo(k)-f<sup>2</sup>uoranthene (Rajkumari et al. 2019). *D. radiouridans* is another important fungus used in bioremediation of radioactively contaminated sites (Brim et al. 2006). *Sulfolobus sulfataricus* secrete lactonase enzyme that acts against organophosphates (Hawwa et al. 2009). *Thermoascus aurantiacus*, another fungal strain, can secrete phenol oxidase and target phenolic hydrocarbons (Machuca et al. 1998).

Rajkumari et al. (2019) studied different approaches of degradation of hydrocarbon waste. *Candida, Aspergillus, Chlorella*, and *Penicillium* were found to be most suitable in the elimination of these wastes. A marine fungal laccase-mediated detoxification and bioremediation of anthraquinone dye called reactive blue was reported (Verma et al. 2012). These laccases could work under very high salinity. Similarly, laccase from *Fusarium incarnatum* was able to degrade bisphenol A, which is a endocrine-disrupting chemical (Chhaya and Gupte 2013). Other studies indicated heavy metal and chloropyriphos bioremediation can be achieved by using *Aspergillus sp, Curvularia*, and *Acrimonium sp*. (Akhtar et al. 2013; Silambarasan and Abraham 2013); likewise, polychlorinated biphenyl degradation can be degraded by *Phoma eupyrena, Doratomyces nanus, Myceliophthora thermophila*, and *D. verrucisporus* (Barghini et al. 2013). Lugowski et al. 1998 has reported that *Pseudomonas sp* is used for degradation of aromatic hydrocarbons. *Halomonas* sp. and *Pseudomonas aeruginosa* strain is used for cleaving of aliphatic hydrocarbons.

## 15.2.7 Bioactive Peptides from Marine Fungi

Oceans are the biggest resource for novel therapeutic compounds. Thousands of secondary metabolites such as polyketides, lactones, alkaloids, steroids, and peptides having pharmacological significance are discovered from marine fungal strains (Jin et al. 2016). Sessile marine microorganisms usually harbor the fungal strains in a symbiotic relationship where the marine fungi protect the host against predators and disease by releasing bioactive compounds (Schueffler and Anke 2014). The unique structural and functional diversity of the marine bioactive compounds is attributed to the extreme conditions of salinity, pressure, and temperature that also give immense stability from all kinds of degradation to these peptides, making them promising candidates for drug discovery. Thus, isolating and characterizing novel bioactive peptides and metabolites from marine fungi with therapeutic properties is a promising avenue to explore in the prevention of human diseases. To date, thousands of compounds have been isolated from many marine fungi, but curating them all is not feasible. So, the data from two latest reviews covering last 15 years of research (Ibrar et al. 2020; Youssef et al. 2019) on the fungal bioactive peptides and compounds is adapted and a comprehensive summary is presented in Table 15.1 with additions and modifications made according to the relevance and scope of this chapter.

#### 15.2.7.1 Peptides

In the last five decades, a significant number of marine bioactive peptides are discovered that either fall in the class of synthetic, non-ribosomally produced peptides such as bacitracins, polymixins, glycopeptides, or gramicidins, etc., or natural, ribosomal peptide class. The synthetic peptides are mostly produced by bacteria, but natural peptides are produced by many species including marine fungi with potent activities (Saleem et al. 2007). Many fungi belonging to various genus produce peptides showing antimicrobial, antiviral, potent cytotoxic, antitumorigenic, antidiabetic, anti-inflammatory, lipid-lowering activities. These peptides are structurally diverse from being cyclic to N-methylated. Some are dipeptides, nonapeptides, depsipeptides, or pentadecapeptides having complex backbones and many side chains. Genus Aspergillus is found to be a rich source of bioactive peptides with Aspergellicins A-E, Cyclodipeptide, Sclerotide A-B, Terrelumamide A-B, Psychriphillin E-G, Aspersymmatide A, Cotteslosin A, Diketopiperazine dimer, cyclic tetrapeptide, Aspergellipeptide D-E, and 14-hydroxycyclopeptine being produced by them showing cytotoxic, anticancer, and anti-inflammatory properties (Table 15.1). Cordyhehptapeptides and efrapeptins are certain other bioactive peptides isolated from Acremonium sp with cytotoxic and antibacterial activities. Lajollamide A from Asteromyces, Dictyonamide A from Certodictyon, Clonostachysins from Clonostachys, and Ungusin A, Emercellamide Emericella Rostratins from *Exserobilium* from SD, and are cytotoxic, antidinoflagellate, and antimicrobial in nature. Similarly, peptides from Microsporum, Penicillium, Scytalidium, Simplicillium, Stachylidium, Talaromyces, and Zygosporium fungi also show various toxic effects on cancers and microbes.

The general procedure for isolating fungal peptides involves culturing of fungi under appropriate conditions and extraction of peptides using solvents such as ethyl acetate. The extracted sample is lyophilized and further purified using chromatographic techniques until pure forms of peptides are obtained. 1D and 2D NMR techniques in combination with mass spectrometry are used to determine the structure of the peptides and Marfey's and Mosher's reactions are used to elucidate the absolute configuration, amino acid composition, and structural modifications (Wang et al. 2017) Biological activity of the purified peptide is measured using  $IC_{50}$ or MIC (minimum inhibitory concentrations) values against cancer cell lines, pathogenic bacteria, and many other microbes.

#### 15.2.7.2 Bioactive Compounds

Marine secondary metabolites have gained a lot of attention in the recent past due to their potent pharmacological properties. The accidental discovery of cephalosporin C antibiotic from the marine *Cephalosporium sp.* fungus in 1949 started a trend to explore marine habitats for bioactive compounds. Many other marine fungi-derived products are currently available in the market such as antibacterial terpenoid fusidic acid, polyketide griseofulvin antibiotic, penicillins, cephalosporins, macrolides, statins, many alkaloids, glycosides, isoprenoids, lipids, etc. (Chandra and Arora 2009; Hamilton-Miller 2008), that exhibit potent toxicity towards tumors, cell proliferation, microtubule formation, pathogenic bacteria, viruses, nematodes, foul

smells, and also exhibit photo-protective activities (Rateb and Ebel 2011). Bioactive compounds are produced by all kinds of extremophilic fungi from psychotolerant, to thermophiles, piezophiles, acidophiles, halotolerant, and xerophiles. Table 15.2 recapitulates different secondary metabolites and their biological activities. Many bioactive compound-secreting fungal strains are discovered by exploring extremely toxic environments such as Berkeley acid lake, hot springs, salt salterns, fumaroles, deep sea sediments and vents, mangroves, Antarctic permafrost, etc. These places have become rich biodiversity for the exploration of such value-added compounds (Ibrar et al. 2020).

Bioactive compounds are also extracted and purified in the same way as peptides, although the characterization techniques will differ. A bioassay-guided fractionation procedure is employed to obtain pure compound fractions, where the potential activity of the fractions is assessed. Most marine compounds have different chemical composition so different polar compounds have to be used for the fractionation method so that the active compound can be separated from the inactive fractions depending on the partition coefficients of the analytes. Polyketides alkaloids, sugars, steroids, and saponins are generally found in aqueous fractions, whereas peptides need mildly polar solvents, and terpenes, hydrocarbons, and fatty acids are found in low-polar fractions. The bioactive fractions are next subjected to gel permeation chromatography to further purify the molecules. The purified compounds are then structurally and chemically characterized by sophisticated techniques such as mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy. High-resolution 1D and 2D NMR spectroscopy are routinely used for the structural characterization of the bioactive compounds.

# 15.3 Conclusion

Biotechnological industries are using a variety of extremophilic fungi as solutions to diverse industrial processes. The survival strategies of extremophilic fungi are unique and associated with the production of extremozymes and various secondary metabolites with robust qualities, making them a rich and abundant resource. Despite their potential, a very small percent of extremophilic fungi are discovered. Exploration of extremophilic organisms will make a huge impact and open new avenues in biotechnology research. With the advancement in various technologies like metagenomics, genetic engineering, in silico analysis, and technology that can access uninhabitable and inaccessible places on earth, it is now possible to identify, isolate, and extract potent compounds that can cater to the needs of almost every sector of the biotech industry to help form a sustainable and efficient biobased economy.

Table 15.2 Bioactive p	eptides and secondary metab	olites isolated from ma	Table 15.2 Bioactive peptides and secondary metabolites isolated from marine fungi, their structure, sources, and biological activities	and biological activities	
Bioactive peptides	Marine fungi	Features	Source	Biological activity	References
Peptides					
Cordyheptapeptide C Cordyheptapeptide C	Acremonium persicinum SCSIO 115	Cyclic heptapeptides	Marine fungus	Cytotoxic and antitumor activity	(Chen et al. 2012)
Efrapeptin $E\alpha$	Acremonium	Pentadecapeptides	Marine fungus	Cytotoxic activity	(Gupta et al. 1992)
Efrapeptin F Efrapeptin G	Tolypocladium niueum Acremonium sp	Polypeptides Polypeptide	Fractionated extract of <i>T</i> . <i>niueum</i>	Cytotoxic activity Cytotoxic and	(Boot et al. 2006)
RHMI	Acremonium sp.	N-methylated linear octapeptides	Cultured from a marine sponge	antibacterial activity Antibacterial activity	(Boot et al. 2007)
Aspergillicins A-E	Aspergillus carneus	Depsipeptides	Estuarine sediment in Tasmania	Cytotoxic activity	(Capon et al. 2003)
Cyclo-(L-Trp-L-Tyr)	Aspergillus Niger EN-13	Cyclic dipeptide	Isolated from the marine brown alga <i>Colpomenia sinuosa</i>	Cytotoxic activity	(Zhang et al. 2010)
Sclerotide A Sclerotide B	Aspergillus sclerotiorum PT06–1	Cyclic hexapeptide	Putian Sea salt field, China	Antifungal activity Antifungal, antibacterial, and cytotoxic activity	(Zheng et al. 2009)
Similanamide	Aspergillus similanensis KUFA 0013	Cyclohexapeptide	Ethyl acetate extracts of marine unknown sponge	Cytotoxic and antitumor activity	(Prompanya et al. 2015)
Terrelumamide A Terrelumamide B	Aspergillus terreus	Linear lumazine peptides	Marine sediments	Improved insulin sensitivity	(You et al. 2015)
Psychrophilin E	Aspergillus sp	Cyclic tropeptide	Isolated from marine brown algae Sargassum	Cytotoxic activity	(Ebada et al. 2014)
Psychrophilin G	Aspergillus Versicolor ZLN-60	Cyclic peptides with anthranilic acid	Marine-derived fungi	Lipid-lowering activity	(Peng et al. 2014)
Aspersymmetide A	Aspergillus Versicolor	Cyclic hexapeptide	Isolated from a gorgonian coral <i>Carijoa</i> sp.	Cytotoxic activity	(Hou et al. 2017)

Table 15.2 (continued)					
Bioactive peptides	Marine fungi	Features	Source	Biological activity	References
Cotteslosin A	Aspergillus versicolor (MST-MF495)	Cyclic pentapeptides	Isolated from Australian beach sand	Cytotoxic and antitumor activity	(Fremlin et al. 2009)
Diketopiperazine dimer Cyclic tetrapeptide	Aspergillus Violaceofuscus	Diketopiperazine dimer Cyclic tetrapeptide	Isolated from marine sponge Reniochalina sp.	Anti-inflammatory activity	(Liu et al. 2018)
Aspergillipeptid D Aspergillipeptid E	Aspergillussp. SCSIO 41501	Cyclic pentapeptide Tripeptide	Isolated from marine gorgonians	Antiviral activity	(Ma et al. 2017)
14-Hydroxy- cyclopeptine	Aspergillus sp. SCSIOW2	Cyclic dipeptide	Isolated from deep sea (1000 m depth) fugus	NO inhibition activity	(Zhou et al. 2016)
Clavatustides A Clavatustides B	Aspergillus clavatus C2WU	Cyclodepsipeptides	Xenograpsus testudinatus Sulphur-rich hydrothermal vents in Taiwan	Cytotoxic and Antitumor activity	(Jiang et al. 2010)
Lajollamide A	Asteromyces Cruciatus	Pentapeptide	Isolated from the Coast of La Jolla, USA	Antibacterial	(Gulder et al. 2012)
Dictyonamide A	Fungus KO63	Linear dodecapeptides	Isolated from marine red alga <i>Ceratodictyon spongiosum</i>	CDK-4 inhibition	(Komatsu et al. 2001)
Clonostachysin A Clonostachysin B	Clonostachys rogersoniana strain HJK9	N-methylated cyclic nona peptides	Isolated from a sponge, Halicondria japonica	Antidinoflagellate activity	(Adachi et al. 2005)
Unguisin A Emericellamide B	Emericella CNL-878	Cyclic depsipeptides	Isolated from co-culture with marine Salinispora arenicola	Antibacterial activity	(Oh et al. 2007)
Microsporin A Microsporin B	Microsporum cf. gypseum	Cyclic tetrapeptides	Isolated bryozoan <i>Bugula</i> sp., Virgin Islands USA	Inhibition of histone deacetylases, cytotoxic and antitumor activity	(Gu et al. 2007)

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Isolated from a neomycin- resistant mutant marine     Cytotoxic activity     (Wang et al. <i>Penicillium purpurogenum</i> 2016)	Soil under a Ribes sp. east of Oksestien, GreenlandAntimicrobial, antiviral, anticancer, and et al. 2005)Oksestien, Greenlandanticancer, and 	Isolated from marine sponge         Antibiofilim activity         (Scopel et al.           Axinella corrugate         2013)	rived fungi Antiviral activity (Rowley et al. 2003, 2004)	rived fungi Cytotoxic activity (Liang et al. Antifouling activity 2017, 2016) Cytotoxic and antitumor activity Antifungal and antiviral activity	a Binding to vasopressin (Almeida et al. receptor 2016) Binding to seratonin receptor	a marine Antibacterial activity (Dewapriya et al. 2018)	ved fungus     Cytotoxic and antitumor     (Oh et al. 2007; Torres-García et al. 2014)
Isolated from a neomyc resistant mutant marine <i>Penicillium purpurogen</i> <i>G59</i>	Soil under a Ribes sp Oksestien, Greenland	Isolated from marii Axinella corrugate	Deep sea-derived fungi	Deep sea-derived fungi	Isolated from a Marine sponge	Isolated from a marine Tunicate.	Marine-derived fungus
Cyclic dipeptide	Cyclic nitropeptide	Dipeptide	Linear, lipophilic Peptides,	Linear peptides	N-methylated peptides	N-methylated linear peptides	Cyclic depsipeptide
Penicillium purpurogenum G59	Penicillium algidum	Penicillium F37	Scytalidium CNL240 Scytalidium	Simplicillin obclavatum EIODSF 020	Stachylidium sps.	Talaromyces sps,	Zygosporium masonii
Penicimutide	Psychrophilin D	Cis-Cyclo (Leucyl- Tyrosyl)	Halovir A Halovirs B–E	Simplicilliumtide A Simplicilliumtide D Simplicilliumtide E, G and H Simplicilliumtide J	Endolide A Endolide B	Talaropeptide A Talaropeptide B	Zygosporamide

Table 15.2 (continued)					
Bioactive peptides	Marine fungi	Features	Source	Biological activity	References
Secondary metabolites					
Fuscin, dihydrofuscin, dihydrosecofuscin, and secofuscin	Oidiodendron griseum UBOCC-A-114129	Polyketide	765 m below the seafloor	Antibacterial, inhibited CLK1 kinase	(Navarri et al. 2017)
Cytochalasin D	Endophytic fungi <i>Xylaria</i> sp	Polyketide amino acid hybrid	From marine seaweed Bostrychia tenella	Antitumor and antibiotic	(de Felício et al. 2015)
Pentacyclic cytochalasin	Diaporthaceae sp PSU-SP2/4	Polyketide amino acid hybrid	Isolated from the marine sponge	Antibacterial	(Khamthong et al. 2014)
Sterigmantocystin	Aspergillus sp	Polyketide derivative	Marine algae derived, Germany	Cytotoxic	(Ebada et al. 2014)
Rugulosin and skyrin	Pencillium Chrysogenum	Polyketides	Marine benthic-derived Antarctic lake	Antimicrobial	(Brunati et al. 2009)
Malbranpyrroles A-F	Malbranchea sulfurea	Polyketides	Fumerole soil	Cytotoxic	(Yang et al. 2009)
Myceliothermophins A-E	Myceliophthora thermophila	Polyketides containing tetramic acid	Fumarole soil	Cytotoxic	(Yang et al. 2007)
Xanthone and chromone	Penicillium sp. SCSIO Ind16F01	Xanthones and quinolones	Deep sea sediments	Cytotoxic and antimicrobial	(Liu and Kokare 2017)
Anthraquinone	Penicillium sp. OUCMDZ 4736	Polyketide	Sediment roots of mangrove	Antiviral	(Jin and Kirk 2018)
Anthraquinone	Aspergillus Versricolor	Polyketide	Deep sea	Antimicrobial	(Wang et al. 2017)
Azophilones	Pleurostomophora sp	Polyketides	Acidic Berkeley lake	Antimicrobial	(Stierle et al. 2015)

Berkeley lactones	Penicillium fuscum and P. camembertii / clavigerum	Cyclic macrolides	Acidic Berkeley lake	Antimicrobial	(Stierle et al. 2017)
Purpurquinones A-C	Penicillium purpurogenum JS03–21	Polyketides	Red soil from Yunnan, China	Antiviral	(Wang et al. 2017)
Pennicitrinone C	Penicillium citrinumB- 57	Citrinin dimers	Jilantai salt field	Antioxidant	(Lu et al. 2008)
Terraquinone	Aspergillus sp	Curvularian derivative	Sonoran Desert	Cytotoxic	(He et al. 2004)
Paecilin E	Neosartorya fennelliae KUFA 0811	Dihydrochromone dimer	Marine sponge-associated fungus	Antimicrobial	(Kumla et al. 2017)
Curvularin derivatives	Penicillium sp. Sf-5859	Lactone polyketide	Marine sponge-associated fungus	Anti-inflammatory	(Ha et al. 2017)
Graphostrin A	Graphostroma sp. MCCC 3A00421	Chlorinated polyketide	Deep sea hydrothermal sulfide deposits	Anti-allergic	(Niu et al. 2018)
Berkeleydioneand berkeleytrione	Penicillium sp	Polyketide- terpenoid hybrid	Acidic Berkeley lake	Cytotoxic	(Stierle et al. 2004)
Berkazaphilones A-C and many other polyketides	Penicillium rubrum	Polyketide metabolites	Acidic Berkeley lake	Cytotoxic	(Stierle et al. 2012)
Phomopsolides	Penicillium clavigerum	Polyketides	Alga associated from acidic Berkeley lake	Cytotoxic	(Stierle et al. 2014)
Eremophilanetype sesquiterpenes	Penicillium sp. PR19N-1	Sesquiterpenes	Prydz Bay, Antarctica	Cytotoxic	(Lin et al. 2014) (Wu et al. 2013)
Purpurides B and C	Penicillium purpurogenum JS03–21	Sesquiterpene esters	Red soil from Yunnan, China	Antiviral	(Wang et al. 2017)
					(continued)

Bioactive peptides	Marine fungi	Features	Source	Biological activity	References
Indole-diterpinoids	Penicillium camemberti OUCMDZ-1492	Terpenes	Rhizospora apiculata roots from acid niche, China	Antiviral	(Fan et al. 2013)
Penicilliumin B	Penicillium sp. F00120	Methylcyclopent- enedione sesquiterpene	Deep sea sediment	Antioxidant and antiallergic	(Lin et al. 2014)
Spirograterpene A	Penicillium granulatum MCCC3A00475	Spiro tetracyclic diterpene	Deep sea sediment	Antiallergic	(Niu et al. 2017)
Bisabalone sesquiterpenes, and coumarin	Penicillium sp.	Terpenes	Acidic Berkeley lake	Cytotoxic	(Stierle et al. 2004)
Berkeley acetals A-C	Penicillium sp.	Meroterpenes	Acidic Berkeley lake	Cytotoxic	(Stierle et al. 2007)
Berkidrimanes A and B	Penicillium solitum	Drimane sesquiterpenes	Acidic Berkeley lake	Cytotoxic	(Stierle et al. 2012)
Gliotoxin	Aspergillus SCSIO Ind09F01	Diketopiperazine alkaloids	Deep sea	Cytotoxic and antibacterial	(Luo et al. 2017)
Aspochalasins I, J, and K	Aspergillus flavipes	Cytochalasans alkaloids	Rihizospere of plant Sonoran Desert	Cytotoxic	(Zhou et al. 2004)
Globosumones A - C	Chaetomium.Globosum	Orsellinic acid esters alkaloids	Endophytic fungi from Sonoran Desert	Cytotoxic	(Bashyal et al. 2005)
Terremides A-B	A terreus PT06–2	Terremides	Putian salt field	Antimicrobial/antiviral	(Wang et al. 2011)
Indole 3 ethanamide	Aspergillus.Sclerotiorum sp. PT06–1	Alkaloid	Putian salt field	Cytotoxic	(Wang et al. 2011)
Variecolorquinones A-B	Aspergillus.variecolorB- 17	Quinone alkaloid	Jilantai salt field	Cytotoxic	(Wang et al. 2007)
Asperentin B	Aspergillus sydowii	Alkaloid	Deep sea	Tuyosine phosphatase inhibitor	(Wiese et al. 2017)

Table 15.2 (continued)

Tyrosine derivatives	Pithomyces sp	Aromatic alkaloids	Acidic Berkeley lake	Antihypertensive and antimigraine	(Stierle et al. 2007)
Berkeley amides A– D	Penicillium sp.	Amide	Acidic Berkeley lake	Cytotoxic	(Stierle et al. 2008)
Glionitrin A	Aspergillus fumigatus KMC-901and A. sphinogomonas KMK 001	Diketopiperazine disulfide	Acid mine drainage	Cytotoxic and antimicrobial	(Park et al. 2009)
Talathermophilins A and B	Talaromyces. Thermophilus YMI–3	Prenylated Indol alkaloids	Hot spring	Nematocidal	(Chu et al. 2010)
Thermolides	Talaromyces. Thermophilus YM3–4	Macrocyclic PKS-NRPS hybrids	Hot spring	Nematocidal	(Guo et al. 2012)
Dichotomocejs A-D	Dichotomomyces. Cejpii F31–1	NRPS hybrid dichotomocej A	Marine-lobophytum crissum derived	Cytotoxic	(Chen et al. 2017)
Brevianamides/ Mycochromenic acid	B.brevicompactum DFFSCS025	Alkaloids	Deep sea sediment	Cytotoxic/antifouling	(Xu et al. 2017)

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