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MINI-REVIEW

Fungal biodiversity to biotechnology

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Abstract Fungal habitats include soil, water, and extreme environments. With around 100,000 fungus species already described, it is estimated that 5.1 million fungus species exist on our planet, making fungi one of the largest and most diverse kingdoms of eukaryotes. Fungi show remarkable metabolic features due to a sophisticated genomic network and are important for the production of biotechnological compounds that greatly impact our society in many ways. In this review, we present the current state of knowledge on fungal biodiversity, with special emphasis on filamentous fungi and the most recent discoveries in the field of identification and production of biotechnological compounds. More than 250 fungus species have been studied to produce these biotechnological compounds. This review focuses on three of the branches generally accepted in biotechnological applications, which have been identified by a color code: red, green, and white for pharmaceutical, agricultural, and industrial biotechnology, respectively. We also discuss future prospects for the use of filamentous fungi in biotechnology application.

Keywords Filamentous fungi · Biotechnology · Bio-based products · Bioenergy · Biodiversity

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Introduction

"The international community is increasingly aware of the link between biodiversity and sustainable development. More and more people realize that the variety of life on this planet, its ecosystems and their impacts form the basis for our shared wealth, health and well-being" (Ban Ki-moon, Secretary-General, United Nations; in SCBD 2014). These words show that Earth's biological resources are vital to humanity's economic and social development. The Convention on Biological Diversity (CBD) established the following objectives: (i) conservation of biological diversity, (ii) sustainable use of its components, and (iii) the fair and equitable sharing of the benefits arising out of the utilization of genetic resources (SCBD 2014).

The diversity of biomes in the world results in a great richness in flora, fauna, fungi, and microorganisms. With about 100,000 species described so far (Hibbett et al. 2011), studies on fungal biodiversity propose that the actual number of fungus species may be 1.5 million (Hawksworth 2001), between 3.5 and 5.1 million species (O'Brien et al. 2005), or as few as 712,000 species (Schmit and Mueller 2007). Fungi are ancient organisms of great importance because (i) they are the primary decomposers in all terrestrial ecosystems and play critical ecological roles in the global carbon cycle and in nutrient recycling; (ii) they are essential to the survival of many groups of organisms with which they associate (mutualism); (iii) many fungi are human, plant, or animal pathogens; (iv) they are well-developed genetic model systems for molecular biologists; (v) they are of significant potential for agriculture; and (vi) they show great potential for biotechnology and biological production (Baker et al. 2008). The phyla of fungi are the Chytridiomycota, Blastocladiomycota, Neocallimastigomycota, Zygomycota, Glomerulomycota, Ascomycota, and Basidiomycota (Hibbett et al. 2007; James

et al. 2006; Lutzoni et al. 2004). From a total of 3974 entries (project type: ChIP sequencing, genome fragments, resequencing, transcriptome, transposon mutagenesis sequencing, and whole genome sequencing) from the fungus kingdom in the Genomes OnLine Database (GOLD), GOLD release v.5 (Reddy et al. 2015; https://gold.jgi-psf.org/; access in 10/07/2015), 64.2 % belong to the phylum Ascomycota, showing that the genomes of other phyla of fungi have not been greatly studied.

Biotechnology is a platform where bio-based products using organisms, cells, or cellular components to produce new technologies, tools, and products are developed. There currently exist four branches generally accepted in biotechnological applications, which have been identified by a color code: red (health, medical, diagnostics, pharmaceutical products), green (agricultural, food and feed production, environmental biotechnology—biofuels, biofertilizers, bioremediation, geomicrobiology), white (gene-based bioindustries), and blue (aquaculture, coastal, and aquatic/marine biotechnology) (DaSilva 2004).

Filamentous fungi are an important source of genes and metabolic pathways used to synthesize a wide range of economically significant compounds, including peptides, enzymes, vitamins, organic acids, antibiotics, and other substances of relevance to the pharmaceutical, food, feed, chemical, and biotechnological industries (Andersen 2014; Lange 2014). Chambergo et al. (2012) show that the TrMnSOD enzyme from *Trichoderma reesei* is stable and maintains its biological activity from 20 to 90 °C at pH 8 to 11.5 for 1 h, suggesting that it may be a powerful biotechnological tool with many applications (Bafana et al. 2011). The biotechnological importance of filamentous fungi has promoted an interest towards understanding the fungal genome to identify the genomic network and metabolic potential. The biology of fungi can be better understood through the study of biodiversity, the use of "omics," and molecular/bioinformatics tools. Filamentous fungi are important organisms as production platforms in the biotechnological industry. Here, we show the biodiversity of filamentous fungi that have been studied to date, with a focus on the production/identification of compounds/biomolecules for red, green, and white biotechnology, over the period 2000–present. Table S1 shows more than 250 fungal species that have been studied for production of different molecules with potential biotechnology application. We also discuss the future scope and prospects of commercial biotechnological production of these natural products.

Habitats and genomics

Fungi are widely distributed in all habitats and ecosystems on Earth, and many fungi can adapt to extreme environmental conditions of water, wastewater, oxygen, metals, organic/inorganic compounds, temperature, pH, and salinity. Tedersoo et al. (2014) identified soil-inhabiting fungi in 365 global soil samples from natural ecosystems and showed that the geographic range of fungal taxa increased toward the poles and that fungal endemicity was particularly strong in tropical regions, but multiple fungal taxa had cosmopolitan distribution.

On the other hand, fungi can be found in special ecological niches: (i) endophytes (all plants in natural ecosystems appear to be symbiotic with fungi) (Rodriguez et al. 2009); (ii) marine fungi (endophytic fungi or fungi associated with marine algae, seagrass, and mangroves; fungi cohabiting with marine invertebrates, especially corals and sponges; and fungi in marine detritus and in marine extreme environments) (Raghukumar 2008); (iii) anaerobic fungi (which inhabit the gastrointestinal tract of mammalian herbivores, for example the phylum Neocallimastigomycota) (Gruninger et al. 2014); (iv) in cold oligotrophic soils from Antarctica (Godinho et al. 2015); (v) in hypersaline environments (Cantrell et al. 2006); (vi) in unusual niches (Antarctic dry valleys, high Arctic glaciers, salt flats and salterns, hypersaline microbial mats, and plant trichomes) (Cantrell et al. 2011); and (vii) areas with naturally higher radiation levels or that are radioactively contaminated (such as space stations, Antarctic mountains, and the Chernobyl exclusion zone) (Dadachova and Casadevall 2008; Dighton et al. 2008; Tugay et al. 2011). Although some fungi inhabit a specific habitat and others occupy a wide variety of environmental conditions, many regions and habitats of the world need to be studied for fungal discovery, especially in the case of microscopic fungi and those that cannot be cultured (Blackwell 2011).

The systematic and organized study of the biodiversity of fungal species found in different countries has allowed not only the collection and identification of species but also bioprospecting. The U.S. National Fungus Collections (BPI) are the repository for over one million fungal specimens (http://nt.ars-grin.gov/fungaldatabases/), and the Kew Fungarium contains an estimated 1.25 million specimens of dried fungus (http://www.kew.org). The CBS culture collections (http://www.cbs.knaw.nl), the American Type Culture Collection (ATCC; http://www.atcc.org), the Fungal Genetics Stock Center (http://www.fgsc.net/), the INCT Virtual Herbarium of Flora and Fungi (http://inct.florabrasil.net/en/), and other national collections are Biological Resource Centers (BRC) and an essential part of the infrastructure of science and biotechnology for the study and preservation of fungi. Soil, water (marine water, freshwater, lakes, rivers, wastewater), and vegetal environments represent rich habitats for fungi. Fungi are a rich source of compounds with great potential as pharmaceuticals, biocatalysts for chiral reactions, nutritional supplements, cosmetics, agrichemicals, biomaterials, and enzymes, where each of these bioproducts has a strong potential market value.

Advances in "omics" tools, sequencing technology, genome mining, and bioinformatics promise to expand the identification and knowledge of new fungi and fungal genomics. The Fungal Genomics Program (http://jgi.doe.gov/fungi) of the US Department of Energy (DOE) Joint Genome Institute (JGI), the MycoCosm portal (Grigoriev et al. 2014; http://genome.jgi-psf.org/programs/fungi/1000fungalgenomes.jsf), the 1000 Fungal Genomes Community website (http://1000.fungalgenomes.org/home/), the FungiDB (Stajich et al. 2012), the Ensembl Fungi (http://fungi.ensembl.org/index.html), MycoBank (Robert et al. 2013; http://www.mycobank.org/), and other databases provide access to large amounts of genomics data of individual genomes and efficient analysis of comparative genomics of fungi using web-based analytical tools, to identify genes and unveil the genetic network of fungi. The genome size information, gene number, and ORFs are very important to address a number of questions about the life cycle, development, phylogeny, evolution, taxonomy, and types of metabolism in fungi, while genome studies can address specific questions about fungus hosts and lifestyle. "Omics" studies to discover new genes and unveil the genetic network and the intracellular metabolism of the fungus are important for designing new industrial processes and expanding the industrial potential of fungi in biotechnology.

Tavares et al. (2014) showed that *Gymnosporangium confusum* possesses the largest (893.2 Mbp) and *Mixia osmundae* the smallest (13 Mbp) fungal genomes reported. Fungal genome comparisons show that (i) pathogenic fungi may carry more genes dedicated to secondary metabolism than do saprophytes (Yoder and Turgeon 2001); (ii) fungi exhibit tremendous diversity in the number and variety of carbohydrate-active enzymes (CAZymes; plant pathogenic fungi, in general, contain more CAZymes than saprophytic, symbiotic, and animal pathogens) (Zhao et al. 2013); (iii) three *Trichoderma* species display a remarkable conservation of gene order (78 to 96 %) (Kubicek et al. 2011); (iv) analysis of all annotated genes from four *Aspergillus* species (*A. oryzae*, *A. fumigates*, *A. niger*, and *A. nidulans*) showed that 80–96 % of the genes (depending on the species) are still without verified function (Andersen 2014); and that (v) the expression of the genes encoding the plant cell wall-degrading enzymes is regulated by various environmental, epigenetic, and cellular factors, some of which are common while others are more unique to either a certain fungus or a class of enzymes (Aro et al. 2005).

Different fungal strains are being used in biotechnological processes for production of organic acids (citric, itaconic, lactic, and succinic acids), antibiotics (penicillin), and industrial enzymes (cellulase, xylanase, phytase, and others), among them the ascomycete fungi *Aspergillus*, *Trichoderma*, and *Penicillium*. Genetic analyses show the capability of fungi to produce secondary metabolites (low molecular-mass compounds, which have roles in a range of cellular processes and now have important applications such as production of antibiotics, immunosuppressants, polyketides, nonribosomal peptides, terpenes, and hybrid compounds). However, this capability has been substantially underestimated, because many of the fungal secondary metabolite biosynthesis gene clusters are silent under standard cultivation conditions; the production is strain-specific and environment-dependent, and most derived secondary metabolites are not unveiled from the genome sequence (Van den Berg et al. 2008; Brakhage 2013; Nutzmann et al. 2011). Over the last years, strategies have been successfully applied to activate these silent gene clusters in filamentous fungi (Brakhage and Schroeckh 2011).

To evaluate the biosynthetic potential to produce secondary metabolites, several computational tools have been developed to identify complete secondary metabolite biosynthesis gene clusters or secondary metabolite backbone biosynthesis genes in bacterial and fungal genomes. The available software tools include antibiotics & secondary metabolite analysis shell (antiSMASH, http://antismash.secondary metabolites.org; Medema et al. 2011; Blin et al. 2013; Weber et al. 2015), secondary metabolite unknown regions finder (SMURF, http://jcvi.org/smurf/index.php; Khaldi et al. 2010), cluster sequence analyzer (CLUSEAN, https://bitbucket.org/antismash/clusean/overview; Weber et al. 2009), ClustScan (http://bioserv.pbf.hr/cms/index.php? page=clustscan; Starcevic et al. 2008), structure based sequence analysis of polyketide synthases (SBSPKS, http://www.nii.ac.in/sbspks.html; Anand et al. 2010), NRPSPredictor (http://nrps.informatik.uni-tuebingen.de; Rottig et al. 2011), and natural product searcher (NP.searcher, http://dna.sherman.lsi.umich.edu/; Li et al. 2009).

A careful screening of fungal biodiversity is important, since microorganisms can naturally produce a vast range of compounds. Genome and metabolome research to discover new genes that can be used for the production of novel valuable enzymes, bioactive metabolites, and chemicals will impact biotechnology research at several levels: crop health and security, genetic and enzymatic pathways to compound synthesis or degradation, terrestrial carbon cycling and sequestration, and augmentation of the catalog of bioproducts produced by fermentation processes: biofuels, biochemicals, and biomaterials. The development of processes for large-scale fermentation, recombinant DNA technology, "omics" tools, metabolic engineering, directed evolution, and others are being exploited for the discovery and production of new biomolecules from fungi.

Red biotechnology

The search for compounds with new pharmacological properties (safe, potent, and with broader spectrum) is crucial, especially those applying to new targets and based on different

mechanisms. Compounds of great interest to the pharmacological sector are those that combat pathogens, naturally resistant bacteria and fungi, and microbes that have developed resistance; those that combat tumors, viruses, parasites, and physiological diseases; and those for new biochemical detection methods and diagnostics, therapeutic enzymes, or new metabolic pathways for the production of molecules with novel pharmacological properties. Table S1 shows that fungi are a rich and promising source of novel antibiotics and drugs with antifungal, nematocidal, antiprotozoal, antibacterial, antiplasmodial, and antiviral properties, as well as anti-inflammatory inhibitors, anti-tuberculosis and anticancer drugs, agonists or antagonists at adrenergic, dopaminergic, and serotonergic receptors, and hypercholesterolemia treatment agents.

Antibiotics are the best known secondary metabolites produced by fungi, being defined as low-molecular-weight organic natural products made by microorganisms and that are active at low concentration against other microorganisms (Demain and Adrio 2008). The increase in antibiotic resistance has led to an ever higher need for novel products and new classes of antibiotics, with a focus on ESKAPE pathogens (bacteria with resistance to current antibiotics: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanni*, *Pseudomonas aeruginosa*, and *Enterobacter species*) (Brogan and Mossialos 2013). The current president of the USA, Barack Obama, issued Executive Order 13676 on combating antibiotic-resistant bacteria, while the European Union has implemented the New Drugs for Bad Bugs (ND4BB) program (Outterson et al. 2015), presenting strategies to fight antibiotic resistance and to stimulate research in this area. In addition, the project "Quantitative Biology for Fungal Secondary Metabolite Producers," or in short "QuantFung," has the aim of intensifying the efforts to find novel antimicrobial fungal-derived products (Büttel et al. 2015). However, it appears that, in nature, there are millions of bioactive molecules with antibiotic properties made by fungi awaiting discovery.

Taxol (generic name paclitaxel) is a chemical substance of tetracyclic diterpene lactam, produced in low concentrations (0.01–0.05 %) from the bark of the Pacific yew tree (*Taxus brevifolia*). It is an anticancer drug with a market value of millions of dollars per year (Demain 2007). After the first report by Stierle et al. in 1993, showing the taxol production by an endophytic fungus (*Taxomyces andreanae*), other endophytic fungi were identified as a source of novel bioactive agents for the treatment of different diseases (Strobel and Daisy 2003; Strobel et al. 2004; Newman and Cragg 2015; see Table S1). The search for novel sources of taxol and taxane has led to the isolation of fungi (Heinig et al. 2013; Zhou et al. 2010) as potential species that can increase taxol production (Kusari et al. 2014) and thus meet the great demand for this product. However, other new metabolites with anticancer activity obtained from fungi have been recently reported (see Table S1).

The elevated concentration of plasma cholesterol is a major risk factor for the development of heart disease; thus, the discovery of cholesterol-lowering agents produced by fungi has been welcome to healthcare. Molecules with such properties include the fungal statins, produced by *Penicillium brevicompactum*, *Penicillium citrinum*, *Monascus ruber*, and *Aspergillus terreus*, including lovastatin, pravastatin, and others, which act as inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the regulatory and rate-limiting enzyme of cholesterol biosynthesis in the liver (Tobert 2003; Mulder et al. 2015). Cholesterol-lowering agents are among the most widely prescribed products developed by the pharmaceutical industry.

Cyclosporin A, a drug used in organ transplantation, is obtained from the ascomycetous fungus *Tolypocladium inflatum* and was the first immunosuppressive drug showing acceptable levels of toxicity (Bushley et al. 2013). Halovirs (Rowley et al. 2004), equisetin, and phomasetin (Rai et al. 2009) are bioactive compounds produced by fungi of the genera *Scytalidium* and *Phoma*, useful against the herpes simplex and HIV viruses, respectively. Some examples of the potential displayed by fungi for the production of biomolecules of interest for red biotechnology include the potential therapeutic strategy for neurodegenerative diseases (including Alzheimer's disease) of inhibition or reversal of protein tau aggregation by secondary metabolites from *Aspergillus nidulans* (Paranjape et al. 2014) and the discovery and development of new anti-tuberculosis drugs that have powerful inhibitory effects against *Mycobacterium tuberculosis* (Xiao et al. 2015) and inhibit the growth of the human malaria parasite *Plasmodium falciparum* (El Aouad et al. 2012).

Green biotechnology

Significant advances in research and development of biomass-derived chemicals, bioenergy, and biofuels that aim at the replacement of fossil fuels are an ongoing effort in many countries. Research in reducing the contamination of the environment and increasing food, feed, and agricultural production is currently being undertaken, with focus on the utilization of fungi or fungal enzymes (enzymatic bioremediation) and metabolites.

Cellulosic materials constitute the world's largest source of organic carbon, and fungi reuse or recycle this important source of carbon. Biomass-derived energy has the potential to contribute for the reduction of greenhouse gas emissions and stimulation of rural economies; however, the bottleneck for biofuel production includes recalcitrance of lignocellulose, bioenergy crop domestication, and low oil yields from plants/algae. Sustainable biofuels such as cellulosic bioethanol and

biodiesel are used as fuel for flex-fuel cars or road vehicles by substituting for fossil-based products; in this context, the biomass degradation process uses a biological treatment, in which enzyme mixtures from fungi are used to degrade cellulose and hemicellulose to soluble sugars, which are fermented to ethanol by other microorganisms (see Table S1; Valencia and Chambergo 2013; El Bondkly and El-Gendy 2012; Buaban et al. 2010; Gutiérrez-Rojas et al. 2015; Wan and Li, 2012). The fungi *Cunninghamella japonica* and *Mortierella isabellina* are producers of lipids suitable for manufacturing biodiesel (Sergeeva et al. 2008; Zheng et al. 2012). Production of volatile organic compounds (VOCs) has been identified in fungi with potential use in agriculture, medicine, and industry (Strobel et al. 2001; Strobel 2006), and a number of endophytic fungi have been discovered that produce hydrocarbons (alkanes, branched alkanes, cyclohexanes, cyclopentanes, and alkyl alcohols/ketones, benzenes, and polyaromatic hydrocarbons) with potential use as green chemicals (e.g., mycofumigation; Alpha et al. 2015) and biofuels (mycodiesel; Strobel 2011; Morath et al. 2012; Strobel et al. 2013; Strobel 2014, 2015; Spakowicz and Strobel 2015).

Fungi possess the biochemical and ecological capacity to degrade environmental organic chemicals and to decrease the risk associated with metals, metalloids, and radionuclides, either by chemical modification or by influencing chemical bioavailability (Harms et al. 2011). In several fungi, the metabolical ability to transform and/or mineralize a great range of pollutants has been demonstrated (Teeri 2004), such as (a) polycyclic aromatic hydrocabon (PAH) in *Phanerochaete chrysosporium*, *Cunninghamella elegans*, *Penicillium sp.*, *Trichoderma viride*, *Alternaria tenuis*, and *Aspergillus terreus*; (b) benzene, toluene, ethylbenzene, and xylene (BTEX) in *P. chrysosporium* and *Cladophialophora sp.*; (c) chlorophenol in *Coriolus versicolor*, *Trametes villosa*, *Panus tigrinus*, *Bjerkandera adusta*, *Trametes versicolor*, and *P. chrysosporium*; (d) munitions waste in *P. chrysosporium*, *Acremonium sp.*, *Trichoderma lombrachiatum*, *Fusarium*, *Acremonium*, *Cylindrocarpon*, *Gliocladium*, *Trichoderma*, *Penicillium janczewskii*, and *Penicillium sp.*; (e) pesticides in *P. chrysosporium*, *P. ostreatus*, *Phellinus weirii*, *C. versicolor*, *Hypholoma fasciculare*, *Botrytis cinerea*, and *Sordaria superba*; (f) heavy metals in *Aspergillus*, *Alternaria*, *Geotrichum*, *Fusarium*, *Penicillium*, *Trichoderma*, *Rhizopus*, and *Monilia*; (g) raw oil in *Rhodosporidium*, *Rhodotorula*, *Trichoderma*, and *Trichosporon*; (h) radionuclides in *Hormoconis resinae*, *Cladosporium cladosporioides*, *Penicillium roseopurpureum*, *Rhizopus arrhizus*, *Aspergillus niger*, *Penicilium italicum*, *Penicillium acrysogenum*, and others; and (i) pharmaceutical and personal care products (PPCPs) in *Bjerkandera sp. R1*, *Bjerkandera adusta*, and *Phanerochaete chrysosporium* (April et al. 2000; Tortella et al. 2005; Zafar et al. 2007; Dighton et al. 2008; Tugay et al. 2011; Rodarte-Morales et al. 2011).

Table S1 shows other important green biotechnology applications of fungi as bioherbicides, in agricultural and horticultural fields, as biocontrol agents of different pathogens and as plant growth promoters (Rai et al. 2009; Tudzynski 2005; Martinez-Medina et al. 2014).

White biotechnology

White biotechnology uses live cells and enzymes to synthesize bio-based products that are easily biodegradable, require less energy, and produce less waste during their production. Enzymes are major contributors to clean industrial products and processes. They show many advantages over chemical processes (e.g., they have high specificity and efficiency, as well as being a safe, cost effective, and environmentally friendly technology). Enzyme-catalyzed processes are gradually replacing chemical processes in many areas of industry, and most industrial enzymes are recombinant forms produced in fungi. Protein engineering, rational design, synthetic biology, and directed evolution have provided important tools for the development of new enzymes or enzymes with improved properties for new areas of application where enzymes have not previously been used. The ability to produce and secrete large quantities of metabolites to the extracellular medium has enabled the use of filamentous fungi for the industrial production of native proteins or homologous/heterologous recombinant proteins. Some filamentous fungi (e.g., *Aspergillus niger*, *Aspergillus melleus*, *A. oryzae*, *T. reesei*, *Rhizopus oryzae*, *Fusarium venenatum*, *Penicillium funiculosum*, *P. emersonii*, *P. chrysogenum*, *P. roqueforti*, *Humicola insolens*; see Table S1) display many advantages, justifying their employment as workhorses for the production of homologous or heterologous proteins. These advantages include easy cultivation, the presence of a good secretory machinery with post-transcriptional modifications typical of eukaryotic proteins, and the fact that they are safe, non-pathogenic organisms for humans (generally regarded as safe (GRAS)) (Schmidt 2004). Table S1 shows the genetic material from fungi (promoter DNA and gene selection markers) used in recombinant expression systems.

Enzymes have applications in many fields, including organic synthesis (peptidases, amidases, acylases, glycosidases), enzymatic bio-analysis (glucose oxidase, lipase, urease, glutamate dehydrogenase), pharmaceuticals (cellulases, proteases, lipases), laundry detergents (proteases 91 %, lipase 6 %, amylase 2 %, cellulase 1 %), the starch industry (amylases, amyloglucosidases, glucoamylases, glucose isomerase), the dairy industry (lipases), the textile industry (amylase, cellulases), the brewing industry (amylases, glucanases, proteinases, amyloglucosidase, β-glucanase), the baking industry (α-amylase, β-xylanase, proteinase), the leather industry (proteases), the pulp and paper industry (β-xylanases, lipases,

cellulases), biomass conversion (cellulases, xylanases, α-arabinofuranosidases, acetyl xylan esterase, α-galactosidases, manganese peroxidase, lignin peroxidase, and laccases), environmental uses (enzymatic bioremediation), electrocatalysts in biofuel cells (hydrogenases, laccases, and other redox enzymes), and others. Approximately 90 % of industrial enzymes are recombinant enzymes; the use of enzymes as detergent additives still represents the largest application of industrial enzymes—proteases, lipases, amylases, oxidases, peroxidases, and cellulases are added to detergents, where they catalyze the breakdown of chemical bonds upon the addition of water (Adrio and Demain 2014).

The global market for industrial enzymes was worth nearly $4.5 billion in 2012 and nearly $4.8 billion in 2013. The market is expected to reach around $7.1 billion by 2018, a compound annual growth rate (CAGR) of 8.2 % from 2013 to 2018. Technical enzymes were valued at just over $1 billion in 2010. This sector will increase at a 6.6 % CAGR to reach $1.5 billion in 2015. The highest sales of technical enzymes occurred in the leather market, followed by the bioethanol market (BCC Research 2014). According to the list of commercial enzymes from the Association of Manufacturers and Formulators of Enzyme Products (AMFEP 2015; www.amfep.org/), the filamentous fungi are the most represented organisms (55 %) and are used for production of 124, 47, and 54 enzymes for food, feed, and technical applications, respectively (see Table S1).

Filamentous fungi have become widely used for the commercial production of organic acids (citric acid, itaconic acid, gluconic acid, L-lactic acid) with a sizable world market (Klement and Buchs 2013; Lotfy et al. 2007; Singh and Kumar 2007; Wu et al. 2011), as well as for the production of fermented foods (Abe et al. 2006), pigments and colorants for the food industry (Mapari et al. 2005, 2009, 2010; Dufosse et al. 2014), and terpenoids for the pharmaceutical industry (Quin et al. 2014).

Biocatalysts (as both isolated enzymes and whole-cell systems) are increasingly being used to assist in synthetic routes to complex molecules of industrial interest. The current US Food and Drug Administration (FDA) regulation protocol requires that the non-therapeutic isomer be nonteratogenic. (Pollard and Woodley 2007). Biocatalysis and biotransformation are alternative tools with great potential for the development of sustainable technologies for the production of chemicals and drugs, which often offer advantages over chemical synthesis as enzyme-catalyzed reactions, or whole-cell-catalyzed reactions are often highly enantioselective and regioselective. They can be carried out at room temperature and atmospheric pressure, thus avoiding the use of more extreme conditions, which could cause problems with isomerization, racemization, epimerization, and rearrangement, with high chemo-, regio-, and enatio-selectivities (Patel 2008). In this context, Borges et al. (2009) and Rodarte-Morales et al. (2011) showed the utilization of fungi as biocatalysts in the synthesis or degradation of molecules.

Concluding remarks and future directions

Fungal natural products have proven to be a rich source of useful compounds having a wide variety of biological activity. In nature, fungi are organisms of great importance, and research is needed to understand their biology, ecology, physiology, and lifestyle, taking into account their wide biodiversity. Problems that may arise during the study of fungi are lack of a sexual life cycle, multinucleate conidia, and large genome size in some species. Hence, it is important to establish national programs for the collection, conservation, and analysis of natural products produced by fungi, in order to identify new industrial enzymes as well as primary and secondary metabolites. Since many species have a wide distribution, the same bioactive compounds may be collected in different regions. The analysis of data from Table S1 shows the potential biotechnological applications of those fungi that have been isolated and studied; however, more studies should establish the ability of fungi to solve the new challenges imposed by a sustainable society.

We have shown that fungi and their metabolic potential can be important for a wide range of biotechnological applications. However, in the next years, the key issues related to the use of fungal biodiversity in biotechnology are (i) developing large-scale biological monomer-recycling systems which are environmentally friendly for biodegradable plastics, such as polybutylene succinate-coadipate (PBSA), and for recovery of the component monomers or oligoesters; (ii) identifying new biological catalysts for asymmetric synthesis, since more than half of drug candidate molecules have more than one chiral center; (iii) studies for more precise metabolic engineering of fungi, further eliminating energy- and precursor-competing pathways while improving the flux through the metabolic pathway, which might facilitate further increase in titer and/or yield of the metabolite of interest; (iv) search for novel and potent fungal strains capable of producing new enzymes and secondary metabolites; (v) development of genetic engineering and genome editing tools, of mutant or recombinant strains for protoplast fusion, genetic manipulation of inducer-forming pathways, signaling cascades, and/or activation of transcription of the secondary metabolic gene clusters; (vi) development of conditions of culture, fermentation conditions, and carbon source for increased industrial production; (vii) development of analysis procedures on a large scale to identify fungal producers of metabolites of interest, as well as identifying the structure and function of most of the metabolites encoded by unknown gene clusters; (viii) investigating all habitats in several regions of the world to increase the number of known fungal species, so that isolates

can be available in collections to perform activity assays; (ix) curated and systematic versions of fungus databases, which is important to alleviate the problem of misleading function inferred by sequence homology, since experience shows that manual curation, supplemented with experimental evidence, is still required for absolute accuracy; (x) further study of fungal VOCs, bioluminescent fungi, fungal interaction with other organisms, and epigenetics events, which may represent a new frontier in bioprospecting and the discovery of new products for human exploitation; (x) intensifying collaborations between mycologists, biotechnologists, and molecular biologists to explore the high metabolic potential of fungi; and (xi) driving or modifying metabolic pathways to produce precursors or new metabolites or to humanize the fungal glycosylation pathway.

Globally, plants produce an estimated 200 billion tons of biomass per year in the form of sugars, polysaccharides, oils, and other biopolymers (Vega-Sanchez and Ronald, 2010), representing an unprecedented renewable resource for bioenergy and chemical block production. Fungal biodiversity is a key component of lignocellulosic biorefinery platforms to obtain and explore a list of top sugar-derived building blocks: 1,4-succinic, fumaric, and malic acids; 2,5-furandicarboxylic acid; 3-hydroxypropionic acid; aspartic acid; glucaric acid; glutamic acid; itaconic acid; levulinic acid; 3-hydroxybutyrolactone; glycerol; sorbitol; xylitol/arabinitol (Werpy and Petersen 2004); ethanol; furans; glycerol and derivatives; biohydrocarbons; lactic acid; succinic acid; hydroxypropionic acid/aldehyde; levulinic acid; sorbitol; and xylitol (Bozell and Petersen 2010), as well as building blocks from lignin (power–fuel–syngas, macromolecules, and aromatic compounds) (Holladay et al. 2007). The development and production of bio-based products (biochemicals, biopharmaceuticals, biofuels, biomaterials) has been driven by several forces including high oil prices, consumer preference for renewable and bio-based products, corporate risk management, and government mandates and support. Bio-based chemicals are expected to grow from 2 % of the total chemical market in 2008 to at least 22 % by 2025. This growth will be driven by the replacement of the petrochemical platform or building block chemicals with bio-based alternatives. In 2025, bio-based chemicals will likely contribute over $500 billion annually to the chemical and materials industry (Patel et al. 2006), and various companies worldwide are in the development pipeline of bio-based products that are of commercial interest and/or show strong potential for growth of the market (Jong et al. 2012). The global market for industrial enzymes is expected to reach $4.4 billion by 2015, achieving a compound annual growth rate of 6 %, and a 2010 report from the World Economic Forum estimated that, by 2020, the market for biofuels, bio-based bulk chemicals and plastics, and bioprocessing enzymes will reach $95 billion (Erickson et al. 2012).

In conclusion, the biotechnology benefits include greatly reduced dependence on nonrenewable fuels and other resources, reduced potential for pollution by industrial processes and products, ability to safely destroy accumulated pollutants for bioremediation of the environment, improved economics of production, and sustainable production of existing and novel products (Gavrilescu and Chisti, 2005). Over the last years, biotechnology has experienced unprecedented growth, with bio-based production processes showing an increase in sales volume of basic chemicals and added-value chemicals. The metabolic potential of fungi to grow on a range of substrates and break down and/or produce new products (including novel therapeutic agents—antibiotics, anticancer drugs, antivirals, polyketides—chiral molecules, specialty chemicals not previously identified, biopolymers, and others biomolecules) shows the roadmap of how they can be applied in different color biotechnology areas.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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