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MINI-REVIEW

Mucoromycota fungi as powerful cell factories for modern biorefinery

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Abstract

Biorefinery employing fungi can be a strategy for valorizing low-cost rest materials, by-products and wastes into several valuable bioproducts through the fungal fermentation. *Mucoromycota* fungi are soil fungi with a highly versatile metabolic system that positions them as powerful microbial cell factories for biorefinery applications. Lipids, pigments, chitin/chitosan, polyphosphates, ethanol, organic acids and enzymes are main *Mucoromycota* products that can be refined from the fermentation process and applied in nutrition, chemical or biofuel industries. In addition, *Mucoromycota* biomass can be used as it is for specific purposes, such as feed. *Mucoromycota* fungi can be employed in developing co-production processes, whereby several intra- and extracellular products are simultaneously formed in a single fermentation process, and, thus, economic viability of the process can be improved. This mini review provides a comprehensive overview over the recent advances in the production of valuable metabolites by *Mucoromycota* fungi and fermentation strategies which could be potentially applied in the industrial biorefinery settings.

Key points

- *Biorefineries utilizing Mucoromycota fungi as production cell factories can provide a wide range of bioproducts.*
- *Mucoromycota fungi are able to perform co-production of various metabolites in a single fermentation process.*
- *Versatile metabolism of Mucoromycota allows valorization of a various low-cost substrates such as wastes and rest materials.*

Keywords *Mucoromycota* fungi · Biorefinery · Lipids · Chitosan · Polyphosphate · Pigments · Co-culture · Enzymes

Introduction

Holistic environmental sustainability is the main driving force in the establishment of biorefineries. Biorefineries aim at integrating upstream and downstream processes for maximum utilization of a plethora of biomass substrates (Chowdhary et al. 2018), by supplying a wide range of the bio-based energy and bioproducts in an economically, socially and environmentally sustainable manner.

Fungi are of great interest as biocatalysts in biorefineries, as they naturally can utilize different substrates to produce and secrete variety of compounds for different applications. *Dikarya* fungi (both *Ascomycota* and *Basidiomycota*) are well-known cell factories in white biotechnology and have been identified as powerful plant biomass-degraders for biorefinery processes, while non-*Dikarya* fungi, especially *Zygomycetes*, have been overlooked in many aspects of their biotechnological potential and importance for the industrial applications.

Zygomycetes fungi represent a heterogenous group of mainly saprotrophs, usually found in soil or in an association with plants, higher fungi, animals or humans as opportunistic pathogens. It is thought that *Zygomycetes* have diverged from the remaining fungi before the colonization of land by plants 600–1400 million years ago (Berbee and Taylor 2001; Heckman et al. 2001). These fungi grow primarily as hyphae—long cell filaments which form more complex structures called mycelia. Unlike the so-called 'higher fungi' represented by the *Ascomycota* and *Basidiomycota* which form mycelia with regular cross walls or septa, most *Zygomycetes* fungi form hyphae lacking septa. The *Zygomycetes* fungi form characteristic zygosporangia—a reservoir

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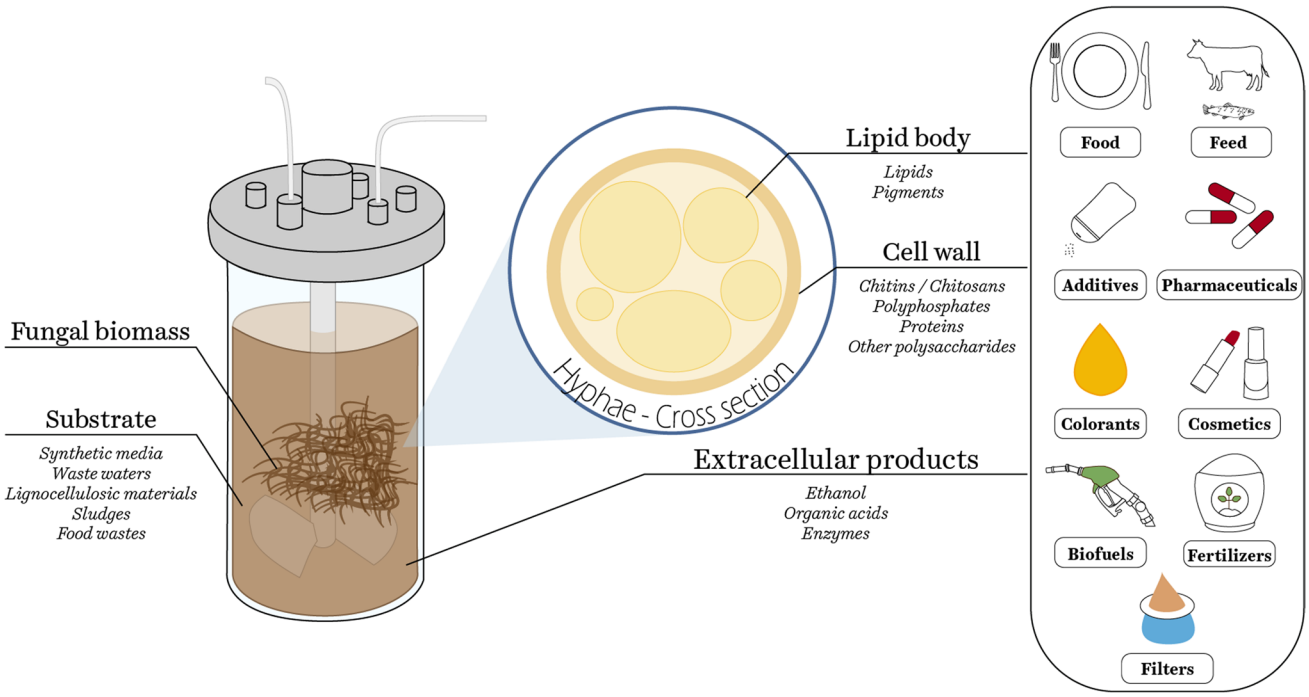

Fig. 1 Overview over the *Mucoromycota* fungi metabolites and their applications

for resistant spherical spores which are formed during sexual reproduction. Zygospore forming fungi have two phyla—*Mucoromycota* and *Zoopagomycota*. *Mucoromycota* are common terrestrial soil fungi and were historically probably among the first land colonizers. There are three subphyla in the phylum *Mucoromycota*—*Glomeromycotina*, *Mucoromycotina* and *Mortierellomycotina*, where *Glomeromycotina* are mycorrhizal fungi, while *Mucoromycotina* and *Mortierellomycotina* fungi are either soil saprotrophic decomposers or can live as endophytes (Pawłowska et al. 2019). Several members of *Mucoromycota* possess dimorphism and can produce two cell forms, budding yeast-like cells and true hyphae. The *Mucoromycota* fungi, often called as 'sugar fungi', grow well on simple sugar substrates, and some of them are able to assimilate more complex organic compounds (Pawłowska et al. 2019). In addition, *Mucoromycota* fungi are characterized by the rapid growth and can secrete and accumulate various compounds. Therefore, these fungi could be considered as powerful cell factories for biorefinery applications.

As for now, fungi-based biorefineries are not sufficiently sustainable and economically viable, especially those that are based on a single product. Reduction of processing steps, time and costs can be achieved through the exploration of *Mucoromycota* fungi potential and by applying co-production concepts along with utilizing low-cost substrates such as rest and waste materials.

In this mini review, we provide an overview over the recent advances in the production of valuable metabolites by *Mucoromycota* fungi and fermentation strategies for application in the industrial biorefinery.

Multifunctionality of *Mucoromycota* biomass

Due to the versatile metabolic system, different *Mucoromycota* fungi are able to produce and accumulate a wide range of valuable metabolites such as (1) lipids, (2) chitin/chitosan, (3) pigments (4) polyphosphates and (5) proteins (Fig. 1). In addition, *Mucoromycota* can simultaneously co-produce several of these metabolites in a single fermentation process. For example, a co-production of lipids and bio-polymers chitin/chitosan (Zininga et al. 2019), lipids and polyphosphate (Dzurendova et al. 2020a), lipids and pigments (Klempová et al. 2020) or even three-product fermentation of rice-straw hydrolysates by *Mucor indicus* into lipids, chitosan and ethanol has been reported (Satari et al. 2016b). Thus, *Mucoromycota* biomass could be fractionated into various products for different markets seeking after raw materials with the specific functionalities or it can be used as whole.

In fact, several studies suggest utilizing *Mucoromycota* as a high value nutritious ingredient directly in animal feed. Thus, Barnharst et al. (2021) suggested *Mucor indicus* and *Rhizopus oryzae* biomass grown on corn-based

wet distiller's grains as value added component of the monogastric animal feed. Karimi et al. (2019) evaluated *Rhizopus oryzae* and other *Mucoromycota* fungi cultivated on vinasse materials as suitable components for protein rich fish feed. The fungus *Rhizopus oryzae* grown on potato protein liquor was recommended as a feed ingredient by Souza Filho et al. (2017). Svensson et al. (2021) utilized the ability of *Rhizopus oryzae* to secrete amylases for valorizing bread residues into mycoprotein rich food and feed, which also contained nutritious fatty acids.

Low- and high-value lipids

Several *Mucoromycota* fungi are known to be oleaginous and able to accumulate from 20 to 80% (w/w) of lipids. Zhao et al. (2020), in an extensive screening study involving over 669 *Mucoromycota* strains, identified fungi from the following genera as oleaginous—*Backusella*, *Cunninghamella*, *Mucor*, *Rhizomucor*, *Dissophora*, *Helicostylum*, *Circinella*, *Ambomucor*, *Rhizopus*, *Actinomucor*, *Gilbertella*, *Lichtheimia*, *Syncephalastrum* and *Absidia*. Among all *Mucoromycota* fungi, *Mucor circinelloides* is often utilized as a model oleaginous filamentous fungus for high- and low-lipid producing strains since it has fully sequenced genome (Tang et al. 2017) and it was the first fungus used for the commercial production of fungal lipids. The work on utilizing *Mucor (javanicus) circinelloides* for industrial lipid production was initiated in 1976 in UK, and the process was commercialized in 1985 by J. & E. Sturge Ltd. in 220 m^3 stirred tank bioreactors producing 2 tons of 'Oil of Javanicus' per batch. The main interest in *Mucor* oil came from the high content of gamma linolenic acid (Kyle 2010; Kyle and Ratledge 1992), but due to the low market demand and high production costs, this process is no longer active.

Usually, *Mucoromycota* lipids have similar fatty acid profile as vegetable oils with mono- and di-unsaturated fatty acids dominating (Ratledge 1993). Some *Mucoromycota* fungi can accumulate essential fatty acids such as gamma-linolenic acid (GLA; 18:3n-6), dihomo-gamma-linolenic acid (DGLA; 20:3n-6) and arachidonic acid (AA; 20:4n-6). Therefore, *Mucoromycota* lipids can be used as food and feed ingredients and in the production of biofuels (Mhlongo et al. 2021; Patel et al. 2020).

Lipids are accumulated in specialized organelles of varying size called lipid droplets (Fig. 2) which are localized intracellularly and closely connected to the endoplasmic reticulum (ER). The lipogenesis metabolism in *Mucoromycota* fungi was discovered several decades ago (Brennan et al. 1975; Ratledge 1988), and there are two principally different lipid accumulation pathways recognized in *Mucoromycota*: (1) de novo lipogenesis, when sugar, glycerol or acid-based substrates are assimilated under nitrogen limitation, and (2) ex novo lipogenesis, when lipophilic carbon source is assimilated during active cell growth and nitrogen limitation is not the strict requirement. Recent advances in omics technologies allow a better understanding of lipogenesis by finding new enzymes and genes which are directly or indirectly involved in the lipogenesis. For example, Chang et al. (2019) recently discovered that overexpression of homologous adenosine monophosphate deaminase (AMPD), activated by nitrogen limitation, promotes a cascade effect that blocks the TCA cycle and leads to a metabolic reorganization of acetyl-CoA towards the lipid synthesis (Fig. 3).

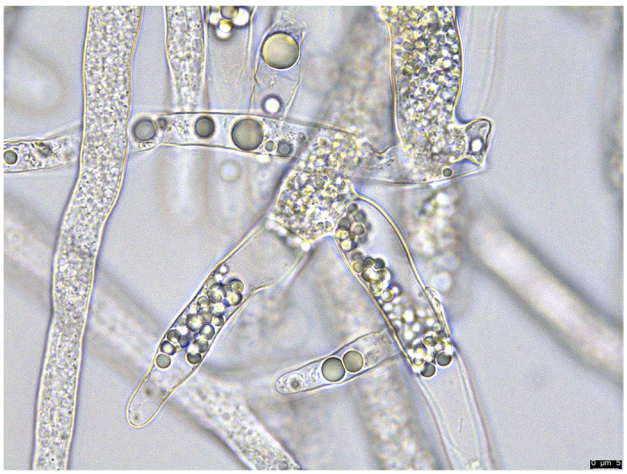

Fig. 2 Hyphae of *Mucor circinelloides* containing lipid bodies. Author: Simona Dzurendova

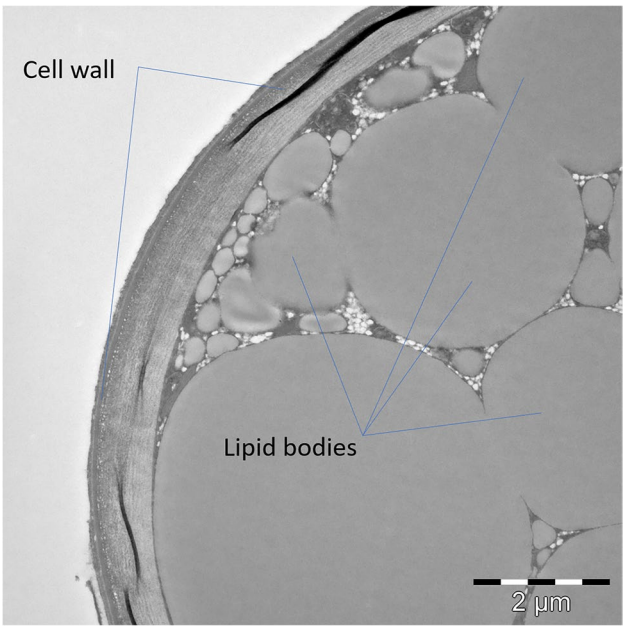

Fig. 3 A cross section of lipid-rich *Mucor circinelloides* hypha visualizing cell wall containing chitin and chitosan. Author: Lene Cecilie Hermansen

Wang et al. (2020) described the importance of tetrahydrobiopterin (BH_4), a well-known cofactor of nitric oxide synthase and phenylalanine hydroxylase, in the lipogenesis of *Mortierella alpina*. Increased BH_4 levels promote complex coordination of glycolysis through the pentose phosphate pathway, TCA cycle and the folate-mediated one-carbon pathway to NADPH production for lipid synthesis and unsaturation. Tang et al. explored the effect of beta-isopropylmalate dehydrogenase, an enzyme involved in the branched-chain amino acid pathway (BCAA), on the lipogenesis of *Mortierella alpina* (Tang et al. 2021) and *Mucor circinelloides* (Tang et al. 2020). It was demonstrated that the overexpression of this enzyme can lead to an increase in the total fatty acids by 20% and 70% for *Mortierella* and *Mucor*, respectively. The suggested mechanism is that this enzyme functions as a bypass of the BCAA pathway to lipogenesis via other metabolic pathways.

Due to the presence of both de novo and ex novo lipogenesis, Mucoromycota can utilize a wide range of carbon sources, which positions them as an attractive lipid-producing cell factories for biorefineries, and it is well described by Demir and Gündes (2020) in their recent review article. In this mini review, we present a modified version of the table from Demir and Gündes (2020) article (Table 1S), providing overview over utilization of different carbon sources by *Mucoromycota* and examples of waste recovery. Some genera, as, for example, *Mucor*, show the highest assimilation rate for glucose, while several *Mortierellas* possess the best assimilation rate for maltose (Demir and Gündes 2020). It has been reported that utilizing different carbon sources by *Mucoromycota* fungi allows to produce lipids with the targeted unsaturation. For example, some studies indicate that the utilization of sucrose by *Mucor circinelloides* can provide higher content of monounsaturated lipids, while starch resulted in more polyunsaturated lipids (Carvalho et al. 2018).

In contrast to pure monomeric sugars for oil production, hydrolysates from lignocellulosic materials are cheaper, sustainable and an abundant alternative. Numerous types of lignocellulose hydrolysates were shown to be suitable for fermentation by *Mucoromycota*, such as sugarcane bagasse by *Mortierella wolfii* (Hashem et al. 2021), *Mucor circinelloides* (Carvalho et al. 2019, 2018) and *Mucor indicus* (Satari et al. 2016b); or rice hulls and corn stover hydrolysate by *Mortierella isabellina* (Economou et al. 2011; Ruan et al. 2012). Furthermore, in a recent work, *Mucor circinelloides* was engineered to improve the tedious xylose assimilation (Zhang and Song 2021) and enhance the utilization of all available sugars in hydrolysates.

On the other hand, valorization of rest- and waste materials represents a great opportunity for economical sustainability of single cell oil production. Potato, chicken and pork pulp rest materials were used as carbon and nitrogen source to support growth and lipid production of *Mucor circinelloides* (Tzimorotas et al. 2018). Other examples following the same approach can be found with potato processing wastewater (Muniraj et al. 2015), cheese whey permeate (Chan et al. 2018), pear pomace (Fakas et al. 2009) or wheat sorghum (Economou et al. 2010). Rest and waste materials can be also used as lipid source to be transformed into more valued lipids by ex novo lipogenesis. Olive mill wastewater (Bellou et al. 2014), animal fat residues (Slaný et al. 2020b) and waste cooking oils (Kamoun et al. 2019) are good examples of alternatives to the lipid supplementation with alimentary vegetable oils (Čertík et al. 1997; Klempová et al. 2020; Vadivelan et al. 2017).

Besides the high versatility in carbon source assimilation, *Mucoromycota* fungi can use various nitrogen sources such as organic yeast extract and inorganic ammonium sulphate, nitrates or urea. Among the different waste-based nitrogen sources, urea could be a potential renewable and sustainable nitrogen substrate as it comes as a waste or by-product in different bioprocesses. Also, urea as a nitrogen source can provide high biomass and lipid yields, as it was shown for *Mortierella alpina* (Li and Jin 2020). Other media components, such as phosphates, metals ions and trace elements have shown strain specific effects on the *Mucoromycota* lipid production and accumulation (Dzurendova et al. 2020b, 2020c). An interesting observation was obtained when studying the influence of calcium (Ca) ions, the absence of it had a positive effect on lipid accumulation for several *Mucoromycota* fungi (Dzurendova et al. 2021). It was hypothesized that Ca deficiency influences the antilipolytic pathways via calcium-sensing receptors. Eventually, a lack of Ca ions in the endoplasmic reticulum changes the distribution of sterol/cholesterol, which could potentially lead to the activation of sterol-binding proteins and trigger the synthesis of neutral lipids.

In addition to substrate composition, fermentation parameters such as temperature or pH can be optimized to achieve higher lipid accumulation in *Mucoromycota* fungi. Thus, Mironov et al. (2018) showed that pH 6 and temperature 20–22 °C were optimal for arachidonic acid production in *Mortierella alpina*. Slightly acidic pH 6 was generally suitable for triggering oleaginicity in *Mucoromycota*. However, the optimal growth temperature was found to be more strain specific, ranging from 15 to 30 °C (Hashem et al. 2021; Kosa et al. 2018; Zhang and Song 2021).

Chitin and chitosan

Mucoromycota fungi have a unique cell wall structure. Most fungi have chitin as the main structural polysaccharide of their cell wall, which consist of β-1,4 bound *N*-acetyl glucosamine (GlcNAc). In addition, *Mucoromycota* fungi synthesize chitosan, the deacetylated homopolymer of chitin.

The synthesis of chitosan is catalyzed by the polymerization of UDP-GlcNAc monomers by chitin synthase, followed by the enzyme chitin deacetylase which deacetylates the *N*-acetamido group of chitin (Davis and Bartnicki-Garcia 1984; Jones et al. 2020). Then, the chitosan polymer chain forms microfibrils that are embedded in an amorphous matrix consisting of proteins, glucans that putatively cross-link the chitosan fibers, mannoproteins and lipids.

Both chitin and chitosan have applications in medicine, agriculture and wastewater cleaning industries (Jones et al. 2020; Ravi Kumar 2000). While chitin has poor solubility, the cationic amino groups of chitosan make it easily soluble (Jones et al. 2020). Due to chitosan biocompatibility, biodegradability, hemostatic activity, healing acceleration properties, nontoxicity and antimicrobial properties, it is a very attractive biopolymer for medical and cosmetic applications (Martău et al. 2019). Currently, chitosan is produced commercially by high-temperature acid and alkali treatment of crustacean's rest materials (Ghormade et al. 2017). Fungal chitin and chitosan have several advantages over the marine analogue, such as homogenous polymer length, high degree of deacetylation and solubility. Moreover, its production does not depend on the season, requires less use of chemicals and generates less wastes (Beheshti and Karimi 2016; Jones et al. 2020; Tan et al. 1996). Therefore, in recent years, the production of chitin and chitosan from fungal sources has gained a great attention.

Mucoromycota fungi are among the few organisms capable of naturally producing chitosan, accounting 1 to 10% of the dry weight of the cells (Mohammadi et al. 2013; Tan et al. 1996; Ghormade et al. 2017). The most promising chitosan producers belong to the order *Mucorales* and genera *Mucor*, *Absidia*, *Rhizopus*, *Cunninghamella* and *Phycomyces* (Abo Elsoud and El Kady 2019; Ghormade et al. 2017; Hu et al. 2004; Kim et al. 2001; Miyoshi et al. 1992; Tan et al. 1996). The most studied chitosan-producing species is *Mucor rouxii* (also known as *Mucor indicus*, *Amylomyces rouxii* or *Mucor circinelloides*), particularly the *Mucor rouxii* IM80 strain (Bartnicki-Garcia and Nickerson 1962; Safaei et al. 2016; Sues et al. 2005; White et al. 1979). Among the two cell forms of *Mucoromycota*, the filamentous form shows higher content of chitosan than yeast-like form. Thus, it has been reported that cultures consisting of only hyphae cells provided the highest chitosan content for *Mucor hiemalis* and *Mucor rouxii* (Beheshti and Karimi 2016; Lennartsson et al. 2009).

Several strategies have been used to increase the yield of chitosan in *Mucoromycota* fungi, where the most relevant variables are limitation of phosphorus, low pH, usage of organic nitrogen sources and supplementation with trace elements and plant hormones. Limitation of inorganic phosphate (Pi) combined with acidic pH has been shown to increase chitosan yields in *Mucor rouxii* (Mohammadi et al. 2013; Safaei et al. 2016) and several other *Mucoromycota* fungi (Dzurendova et al. 2020a). The absence or the addition of small amounts of inorganic phosphorus in yeast extract-based growth media can result in the highest chitosan yield in *Mucor rouxii*. Using a complex organic nitrogen source such as yeast extract enhances both chitosan and biomass production, and it has been shown that 5 g/L of yeast extract is suitable to obtain the highest yield of chitosan in *Mucor rouxii* (Safaei et al. 2016). Further, it was shown that metal trace elements added to the growth medium can have a considerable effect on enhancing biomass yield (Sues et al. 2005), chitin and chitosan content in *Mucor rouxii* (Safaei et al. 2016). Thus, adding zinc and potassium increased biomass yield (Sues et al. 2005), and potassium supplementation provided the highest accumulation of chitosan and chitin (Safaei et al. 2016). Chitosan production in *Mucoromycota* fungi can also be improved by adding plant growth hormones (Chatterjee et al. 2009).

To increase the economic feasibility and sustainability of fungal chitosan production, several co-production strategies can be applied, for example, co-production of chitosan and chitin along with lipids or extracellular products such as ethanol and organic acids (Beheshti and Karimi 2016; Dzurendova et al. 2020a). Furthermore, using low-cost nitrogen sources such as urea or yeast cell rests from beer and wine fermentations could enhance biomass and chitosan yields and decrease the cost of the production process (Abasian et al. 2020; Asachi and Karimi 2013; Karimi and Zamani 2013; Satari and Karimi 2018).

Pigments

Several *Mucoromycota* fungi are able to produce pigments, where carotenoids are predominant. Carotenoids are represented by two groups—carotenes, composed of hydrogen and carbon, and xantophylls, which are oxygenated derivatives of carotenes (Sandmann 1994). Carotenes, and especially β-carotene, known as provitamin A, are the main carotenoid pigment produced by *Mucoromycota*. Fungal carotenoids are considered highly valuable metabolites with diverse commercial applications such as nutraceuticals and colorants for feed, food and cosmetics industry.

In fungal cells, carotenoids work as neutralizers of free radicals for preventing the oxidative stress damage. For example, they can stop the propagation of lipid peroxidation on the membranes (Lopez et al. 2014) or decrease the fluidity of membranes to reduce the oxidative damage controlling oxygen diffusion rate (Subczynski et al. 1991). Carotenes also serve as metabolic precursors of trisporic acid that is relevant for the sexual reproduction of *Blakeslea* spp (Schachtschabel et al. 2008).

Among the different *Mucoromycota*, *Mucor circinelloides* and *Blakeslea trispora* have been reported as two

of the most promising industrial producers of β-carotene (Fraser et al. 1996; Iturriaga et al. 2005; Sahadevan et al. 2013). Industrial β-carotene production with *Blakeslea trispora* requires two separate fermentations with (−) and (+) mating type followed by a co-cultivation step that is costly. This would not be the case with *Mucor circinelloides*, where genetic engineering to improve production is also feasible. Also, carotenoid production was registered for the species *Mucor hiemalis*, *Mucor rouxii*, *Mucor mucedo*, *Phycomyces blakesleeanus* and *Umbelopsis isabellina* (Khanafari et al. 2008; Mehta et al. 1997; Mohamed et al. 2020; Mosqueda-Cano and Gutiérrez-Corona 1995; Sahadevan et al. 2013; Slaný et al. 2020a).

Exposure to light, especially blue light, is considered the main triggering factor for carotenogenesis (Corrochano and Garre 2010; Khanafari et al. 2008). Naz et al. (2020b) examined the effect of light conditions on carotenoid production in *Mucor circinelloides* where it was shown that continuous light illumination triggered carotenogenesis in 2,sevenfold compared to dark conditions. In addition to the light, oxygen and temperature have been reported as factors influencing carotenogenesis as well (Dexter and Cooke 1984; Mosqueda-Cano and Gutiérrez-Corona 1995). Glucose availability and C/N ratio do not have any significant effect on the carotenoid production in wild-type strains, and only some effect of it was recorded for *Mucor circinelloides* transformants, where 2.5% of glucose led to the highest carotenoid production (Csernetics et al. 2011). In our recent study, we have reported that Ca ion availability can be used as a novel factor for triggering carotenoid production (Dzurendova et al. 2021). It has been observed that lack of Ca ions in the growth media leads to a higher carotenoid production in *Mucor circinelloides* and *Amylomyces rouxii* (Dzurendová et al. 2021).

Currently, significant understanding on the metabolic regulation of carotenoids synthesis has been attained (Nagy et al. 2019; Sanz et al. 2011), allowing the optimization of its production through other strategies in addition to culture conditions. Several studies report the use of chemical inhibitors or activators to block or enhance certain steps in carotenogenesis to obtain targeted carotenoids, for example, the use of ionone to activate the β-carotene pathway (Mackinney et al. 1952) or the inhibitor piperidine to stop the carotenoid pathway at the lycopene step (Choudhari et al. 2008). Another approach is to inhibit metabolic pathways that compete for common precursors, for instance, the use of cerulenin and ketoconazole to inhibit the fatty acid and sterol synthesis, which compete against carotenogenesis for the acetyl-CoA and farnesyl diphosphate, respectively (Naz et al. 2020a). It is also possible to boost the production through the genetic modifications on target carotenoid synthesis genes, and such attempts have been done for the overproduction of β-carotene in *Mucor circinelloides* (Zhang et al. 2016) and *Phycomyces blakesleeanus* (Mehta et al. 1997), and lycopene in *Blackeslea trispora* (Wang et al. 2017). Mohamed et al. (2020) reported a natural and significant production of the xanthophylls canthaxanthin, asthaxanthin and zeoxanthin in some *Mucoromycota* isolated species. However, the methodology used is not reliable for its detection and verification; the production of canthaxanthin or asthaxanthin at a reasonable level has only been achieved through genetic modifications in *Mucor circinelloides* (Papp et al. 2013; 2006). Genetic engineering remains the most preferrable approach to improve carotenogenesis in *Mucoromycota* fungi.

Polyphosphates

Polyphosphates are polymers composed of phosphate ions (Pi) that are linked by high-energy phosphor-anhydride bonds. The length of polyphosphate chains in fungal cells varies from several tenths to hundreds of Pi units (Shari'a et al. 2002). Polyphosphate can be localized in different organelles. Cytochemical studies show that it can be found in cell wall (Werner et al. 2007), cell membrane, in trabecular, vacuolar and vesicular structures and dense bodies in cytoplasm (Shari'a et al. 2002). Polyphosphates play several important functions in fungal cells, such as energy and phosphate storage, controlling homeostasis via trapping cations and amino acids, regulation of the hyphal phosphate amount and the protection against environmental stress (Beever and Burns 1981). Polyphosphates located in cell walls and cell surfaces are involved in maintaining the integrity of cytoplasmic membrane and in the phosphorylation of glucose and its derivatives (Tijssen et al. 1985). Accumulation of polyphosphates usually undergoes when a high amount of phosphorus is present in the surrounding environment and the process is called luxury phosphate uptake. The highest rate of phosphorus uptake occurs in the exponential growth phase and leads to an accumulation of polyphosphates (Ye et al. 2015). It has been reported that fungal cells can accumulate more phosphorus than necessary for their survival (Beever and Burns 1981).

Little attention has been given to studying polyphosphate accumulation in fungal cells, and the number of studies reporting optimization of the polyphosphate accumulation in *Mucoromycota* fungi is quite limited or outdated. Ye et al. (2015) identified *Mucor circinelloides* as the most suitable candidate for phosphorus recovery from wastewater, with the maximum phosphorus utilization efficiency of 40% and 7.08% cellular P content. He et al. (2019) reported that *Mucor circinelloides* can be used in phosphorus recovery from dairy manure wastewater. In addition to *Mucor circinelloides*, other *Mucoromycota* fungi showed promising polyphosphate accumulation properties. Thus, a high accumulation of polyphosphate was reported in *Mucor*

racemosus mycelia (James and Casida Jr 1964) and *Cunninghamella elegans* (Lima e Silva et al. 2013). Moreover, we identified in our recent study *Amylomyces rouxii*, *Mucor circinelloides*, *Rhizopus stolonifer* and *Absidia glauca* as phosphorus accumulating fungi (Dzurendova et al. 2020a). Given the future depletion of rock phosphate and the increasing phosphorus pollution in aquatic systems, the exploration and use of the phosphorus accumulating potential of *Mucoromycota* fungi represent an innovative and promising solution. Therefore, further research would be needed to understand the molecular mechanisms of polyphosphate accumulation and optimizing this process in *Mucoromycota* fungi.

Valuable extracellular metabolites of *Mucoromycota* fungi

Extracellular metabolites are valuable products of *Mucoromycota* fungi. Production of extracellular metabolites along with the biomass is one of the co-production concepts suggested when employing *Mucoromycota*. Such co-production process is characterized by the easy and quite straightforward separation of intra- and extracellular co-products in the downstream processing. The main extracellular metabolites of *Mucoromycota* are (1) ethanol, (2) short chain organic acids and (3) enzymes.

Ethanol and organic acids

Mucor indicus and *Rhizopus oryzae* are the main ethanolic *Mucoromycota* reported in the literature (Satari et al. 2016a). In addition to ethanol, *Rhizopus oryzae* can produce high amounts of organic acids, such as lactic, fumaric, malic and succinic acid (Naude and Nicol 2018). When optimizing ethanol production by *Mucor indicus*, several important cultivation parameters were identified—amount of the phosphorus (Aghbashlo et al. 2017); addition of trace elements; carbon sources, with the highest ethanol production on glucose (Sues et al. 2005); or anaerobic conditions that support fermentative reactions in *Mucoromycota* (Sues et al. 2005). The level of dissolved oxygen is an important parameter for the fumaric acid production by *Rhizopus oryzae*, where 30–80% of oxygen saturation and high C/N ratio is required for its optimal production (Deng and Aita 2018; Fu et al. 2010). In the 1940s, fumaric acid was produced at industrial scale by *Rhizopus* fermentation in the USA. This process was replaced by petrochemical industry, and nowadays it is getting more interest due to environmental issues and rise of fuel prices (Roa Engel et al. 2008). Regarding the lactic acid, typical yields are up to 60–80% of assimilated glucose, with the remaining glucose being metabolized into ethanol. One strategy to increase the lactic acid yield is through metabolic engineering, for example, increasing the lactic dehydrogenase levels using plasmid transformation with *ldhA*. This approach can lead to increase pyruvate conversion to lactate in detriment of ethanol production (Skory 2004).

Regarding low-cost substrates, sugar hydrolysates from corn stover (Shafiei Alavijeh et al. 2020), sugarcane bagasse (Ueng and Gong 1982), cassava pulp (Thongchul et al. 2010) or spruce (Lennartsson et al. 2011) have been found to be suitable for ethanol and acid production by *Mucoromycota*. The most recent study performed by Sahlan et al. (2020) suggests a novel process for valorization of oil-palm empty fruit bunch through the simultaneous saccharification and fermentation by *Rhizopus oryzae*. The fungal cells were encapsulated in a calcium alginate polymer to increase their resistance to the low pH and high temperatures required for the saccharification process and, thus, improving ethanol and lactic acid production.

Enzymes

Mucoromycota fungi are well known for their production of extracellular proteases (Yegin et al. 2011), phytases (Gulati et al. 2007), lipases, pectinases, amylases (Alves et al. 2002), xylanases (Hassan et al. 2020), etc. Several examples of enzymes from the *Mucor* species can be found on the market, for example, aspartic proteinases for milk coagulation, lipases for dairy products or pectinases for juice clarification have been produced and used on an industrial scale for many years. The diversity of enzymes and expression levels in each *Mucoromycota* species is related to their lifestyle, as it must interact with and benefit from the surrounding environment. A clear example of this was shown by Lebreton et al. (2019), where different *Mucor* species isolated from different habitats (endophytes, parasites, cheese fermenters, saprotrophs, etc.) were clearly sorted by principal component analysis (PCA) using the number of genes encoding carbohydrate-active enzymes (CAZymes) related to plant cell wall degradation.

Considerable attention was given to cellulase producers as a response to the increased interest in lignocellulosic-based biorefinery and bio-pulping (Ferreira et al. 2013). Generally, *Mucoromycota* fungi are mostly saprotrophs in nature, although they are not directly relevant for lignocellulose material degradation due to their poor ability to break crystalline cellulose. It was reported that the strain *Mucor circinelloides* NRRL 26,519 had a complete system of cellulases (β-glucosidase, endoglucanase and cellobiohydrolase), which make it suitable for the direct saccharification of lignocellulosic materials (Saha 2004). However, the experimental design and the lack of precise data upon cellobiohydrolase presence make this affirmation questionable. Several other works showed that *Mucor circinelloides*

is clearly not efficient in lignocellulose degradation. Thus, approaches like co-culture with truly cellulolytic strains (Takano and Hoshino 2012), supplementation with the specific lacking enzymes (Wei et al. 2013) or with commercial cellulase preparations (Takano and Hoshino 2018) are more suitable. Therefore, literature regarding cellulase production and characterization in *Mucoromycota* is limited to β-glucosidase and endoglucanase.

Several studies explored the ability of *Mucoromycota* to excrete β-glucosidase. For example, the study performed by Takó et al. (2010) reported that fifteen of ninety four *Mucoromycota* strains grown in submerged culture using 1% cellobiose showed β-glucosidase expression over 1 U/mL, for example, *Rhizopus oryzae* NRRL2908 with 28.15 U/mL, *Rhizopus stolonifer* CBS403.51 with 9.92 U/mL and *Rhizomucor miehei* NRRL5282 with 3.7 U/mL. On the other hand, for solid-state fermentation (SSF) using wheat bran at 50% solid content, the best β-glucosidase secretion was from *Gilbertella persicaria* ATCC201107 with 425.4U/g substrate. The reported β-glucosidase expression levels are comparable to the ones observed in the *Aspergillus* fungi, a well-known genus for β-glucosidase production, with activities like 6.6 U/mL for *Aspergillus saccharolyticus* CBS 127,449 or 3.1 U/mL for *Aspergillus niger* (Sørensen et al. 2011). However, possible differences due to the media and the growth rate must be considered.

With regard to the inhibition of β-glucosidase by glucose, the inhibitor constant (K_i) falls into normal values: 8 mM in *Mucor miehei* NRRL 5282 (Krisch et al. 2012), 5.49 mM in *Mucor circinelloides* NBRC4572 (Kato et al. 2013) and 3.68 mM in *Gilbertella persicaria* (Krisch et al. 2010) in comparison with β-glucosidase from *Aspergillus niger* and *Trichoderma reesei* with values of 2.7 mM and 3.25 mM, respectively (Chauve et al. 2010).

For the moment, there has not been reported any *Mucoromycota* strain producing glucose-tolerant β-glucosidases. For example, with *K*i values of 0.8 M and 1.36 M, the strains *Aspergillus unguis* NII08123 (Kooloth Valappil et al. 2019) and *Aspergillus oryzae* CBS12559 (Riou et al. 1998) produce β-glucosidases considered as glucose tolerant.

Studies on the production of endoglucanase by *Mucoromycota* are even more scarce. Some of them explored the kinetics and characteristics of endoglucanase in isolated *Rhizopus oryzae* (Murashima et al. 2002), *Phycomyces nitens* (Shimonaka et al. 2004) and *Mucor circinelloides* (Baba et al. 2005), but more aimed at the heterologous expression in *Escherichia coli* for its use in textile treatments (Shimonaka et al. 2006). Some studies compared the endoglucanase expression in SSF using rice bran and husk with *Rhizopus oryzae* CCT 7560 against *Trichoderma reesei* QM 9414 as reference control (Kupski et al. 2014). The results showed a maximum endoglucanase activity of 5.1 U/mL, which was 30% of the total obtained by *T. reesei*, but with earlier expression at 15 h (5 times) and better thermal stability (10–80 times). Other SSF studies employing *Mucor corticolus* (SZMC 12,031), *Rhizomucor miehei* (SZMC 11,005), *Gilbertella persicaria* (SZMC 11,086) and *Rhizopus niveus* (SZMC 13,625) showed maximum expression between 2 and 6 days of incubation with higher values when using wheat bran mixed with milled corn stalks (1:1) in comparison with milled corn stalks and leaves (Takó et al. 2015), where the best result was from *Gilbertella persicaria* SZMC 11,086 with 74.1 U/g dry solids at second day of incubation.

Cultivation strategies applied for *Mucoromycota* biomass production

Cultivation of *Mucoromycota* fungi in bioreactors can be achieved in two ways—submerged and SSF. Submerged fermentations by *Mucoromycota* are often challenging due to their dispersed mycelial growth leading to the higher viscosity and associated wall growth. In a submerged fermentation process, nutrient and oxygen transfer could be hindered by the high viscosity of the dispersed culture. In addition, some *Mucoromycota* fungi are sensitive to the shear stress caused by stirring, and the cells can deform or break resulting in the lower biomass formation. Therefore, it has been shown that pelletization, for example, by the addition of calcium carbonate and microparticles (microparticle enhanced cultivation-MPEC) can improve *Mucoromycota* fermentation (Karahalil et al. 2019). Pellet growth was reported for *Rhizopus* (Hamzah et al. 2009), *Umbelopsis*, *Absidia*, *Cunninghamella*, *Lichtheimia* and *Mortierella* (Kosa et al. 2018). Furthermore, to improve extracellular product separation in submerged *Mucoromycota* fermentation, immobilization of cells was proposed. Such approach enables a semi-continuous submerged fermentation, where extracellular metabolites can be separated continuously. Zheng et al. (2017) suggested a semi-continuous fermentation process of tobacco wastewater substrate by the immobilized cells of *Rhizopus oryzae*, which produced high-activity extracellular pectinases. Similarly, Struszczyk-Świta et al. (2017) performed a fermentation with cell-immobilized *Mucor circinelloides* for the production of extracellular chitinase and lipase. Compared to physico-chemical remediation methods, *Mucoromycota* fungal cells offer higher conversion activities, better selectivity and lower costs for bioremediation processes (Bokade et al. 2021).

Due to the fact that *Mucoromycota* have a good tolerance to low water activity and are able to excrete a wide range of enzymes (Benabda et al. 2019; Takó et al. 2017), they are suitable candidates for SSF. SSF by *Mucoromycota* can be used to enrich different substrates with biologically active compounds and thus improve their nutritional value (Dulf et al. 2020; Feng et al. 2014). For example, Ibarruri et al.

(2021) suggested a valorization process of fruit and vegetable rest materials by *Rhizopus sp.* fermentation to produce protein rich animal feed. Further, Dulf et al. (2020) proposed a simultaneous enrichment of grape pomace, a waste material originating from wine industry, with gamma-linoleic acid and carotenoids by utilizing SSF process with *Umbelopsis isabellina* and *Actinomucor elegans* as cell factories.

Co-culturing *Mucoromycota* with algae as a novel process for oleaginous biomass production

Currently, there is a growing interest for studying co-culturing of oleaginous fungi and microalgae as a novel CO_2-zero process for oleaginous biomass production. This interest is justified by the ability of filamentous fungi to form pellets that facilitate the harvesting process of microalgae. Moreover, a synergistic co-cultivation can increase biomass, lipid yield and decrease CO_2 release (Rodrigues Reis et al. 2018b). *Mucoromycota* fungi, in this context, are relevant because of their high lipid content and their ability to form pellets. For example, *Cunninghamella echinulata* can efficiently agglomerate with cells of the microalgae *Scenedesmus obliquus* to harvest up to 92.7% of the cells and improve biomass and lipid yield by 2.24 and 1.49-folds respectively (Srinuanpan et al. 2018). The increase in lipid content can be explained by the competition of microalgae and fungi for nitrogen, which leads to a higher accumulation of lipids for both (Zorn et al. 2020). However, it has been shown that pelletization of microalgae by *Mucoromycota* appears to be strain-specific, and that not all *Mucoromycota* species are capable to pelletize microalgae (Gultom and Hu 2013; Srinuanpan et al. 2018). For instance, it was reported that *Rhizopus oryzae* shows little to no interactions with *Synechocystis* sp. (Choi et al. 2016) and it has a negative effect on the microalgal growth. In several studies, it has been described the use of non-pellet-forming *Mucoromycota* together with a carrier matrix to increase the aggregation of filamentous fungi and microalgae. For example, Rajendran and Hu (2016) tested attachment of *Chlorella vulgaris* cells with *Mucor circinelloides* and *Mucor hiemalis* on a polymer-cotton composite matrix, and after 8 days 99% of *Chlorella vulgaris* biomass was aggregated in the form of biofilm. Similar results were obtained in a study by Zorn et al. (2020). The co-culture of *Mucoromycota* and microalgae is a new biomass production process that has direct applications in wastewater treatment and bioremediation. Several examples of such an application have been reported. For example, *Chlorella vulgaris* and *Mucor indicus* showed a complete removal of total ammonia (TAN), phosphorus and nitrogen until 10 mg/mL TAN in a synthetic media mimicking wastewater from intensive aquaculture (Barnharst et al. 2018). Another example is the co-cultivation of *Chlorella vulgaris* and *Mucor circinelloides* on dehydrated thin stillage, which are by-products generated during the ethanol distillation process. Up to 56.4% and 73.9% of the total phosphate and nitrogen content were removed by the formed myco-algae biofilm (Rajendran et al. 2017; Rodrigues Reis et al. 2018a). Such co-culturing approach provided higher nutrient removal and resulted in a higher lipid and biomass content.

Current commercial applications of *Mucoromycota* fungi

Currently, several bioproducts originated from *Mucoromycota* fungi are available on the market:

- Enzymes: for the cheese industry, there are relevant products as the rennin-like protease Marzyme Supreme® (DuPontDanisco, Denmark) from *Mucor miehei*[1] that can be applied, for example, in the Mozzarella Cheese production (Rusdan and Kusnadi 2017); or lipase Palatase®[2] 20000L (Novozymes, Denmark) from *Mucor miehei* for the ripening process. Other commercial lipases available are the Lipase F-AP15 (Amano, Japan) from *Rhizopus* sp. and the Lipase MH 10SD (Amano, Japan) from *Mucor javanicus*,[3].[4] Also, it is possible to find many other enzymes like macerase cocktail Sumizyme® MC, glucoamylase Sumizyme® (Takabio-Shin Nihon Chemical, Japan),[5][6] and amylase Amano Gluzyme 12 (Amano, Japan from *Rhizopus* sp..
- Personal care products: exfoliants with *Mucor miehei* extracts like the Artistry™ Intensive Skincare Renewing Peel[7] (Amway, USA) or the Enzyme Exfoliator[8] (Antoinette Alexander™, USA).
- Lipids: arachidonic acid ARASCO® (Martek Bioscience-DSM, USA),[9] SUN-TGA40S (Suntory Ltd, Japan) or RAO (CABIO Biotech, China) from *Mortierella alpina* are used as constituent of infant formula with FDA-GRAS approval. The market for microbial arachidonic acid for dietary supplements has grown considerably over the last few decades and is expected to remain microbial-based in the future (Mamani et al. 2019). Also,

[1] https://cheeseconnection.net/product/marzyme-supreme-rennet/
[2] https://biosolutions.novozymes.com.
[3] https://www.takabio.com/en/catalogue-enzymes.
[4] https://www.novozymes.com/en.
[5] https://www.takabio.com/en/catalogue-enzymes/
[6] https://www.takabio.com/en/gamme-sumizyme/
[7] Artistry™ Intensive Skincare Renewing Peel | Skin Care | Amway.
[8] https://www.antoinettealexander.com/products/enzyme-exfoliator.
[9] DSM Animal Nutrition & Health | DSM.

microbial oil rich in oleic and y-linolenic acid from *Mortierella isabelina* (Sigma-Aldrich) are available (zu Berstenhorst et al. 2009). In the last decade, Jost Chemical Company (USA) patented a method to co-precipitate arachidonic acid with sodium or potassium salts (US Patent no. US20110237813A1)[10] and started to commercialize the arachidonic acid salt, which facilitate the blending with the other components in infant formula.

- Pigments: asthaxantin from genetic modified *Blakeslea trispora*[11]; β-carotene Betanat® and lycopene Lyconat® (Vitatene-DSM, Spain)[12]from *Blakeslea trispora* or BetaBead™, Lyc-O-Beta™ and BetaCote™ (Lycored, USA) from *Blakeslea trispora*.[13]

Conclusion and future prospects

The versatility of *Mucoromycota* metabolism makes it possible to use these fungi in biorefinery to valorize a wide range of substrates into valuable products such as lipids, biopolymers (chitin/chitosan, polyphosphates), pigments (carotenoids), ethanol, organic acids or enzymes. Further research into co-production and co-cultivation strategies would be required to improve the sustainability of *Mucoromycota*-based fermentations.

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Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

[10] https://patents.google.com/patent/US20110237813h3.
[11] https://www.sigmaaldrich.com/CZ/en/product/sigma/sml0982?context=product.
[12] https://www.dsm.com/corporate/news/news-archive/2011/46–11-dsm-completes-acquisition-of-vitatene-s-a-u.html.
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