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ORGANIC ACIDS PRODUCTION BY FUNGI: METABOLISM, PHYSIOLOGICAL AND ECOLOGICAL SIGNIFICANCE

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The data about pathways of biosynthesis, regulation of metabolism, physiological and ecological functions of organic acids production by fungi of various ecological groups are generalized and analyzed. Metabolism and excretion of organic acids by fungi depend on many factors, including nutrient and mineral conditions, temperature, and various stresses. An increase in the excretion of organic acids, especially oxalic acid by fungi is often a response to stress. Organic acids production by fungi has important ecological and physiological significance because it is related to changing the surrounding microconditions and influencing the biotic and abiotic interactions of microorganisms in community. Organic acids are involved in the formation of mycorrhiza, the processes of plant pathogenesis, and are also one of the key factors in wood decay. The ability to acidification largely determines the geochemical role of fungi and their importance in the weathering of rocks and the processes of primary soil formation.

Keywords: heavy metals, metabolism, micromycetes, macromycetes, organic acids, stress, trophic conditions

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INTRODUCTION

Low molecular weight organic acids (LMWOAs) – one of the most important molecules in energy metabolism and regulators of metabolic processes in the cells of living organisms. LMWOAs are of fundamental importance for formation of precursors for amino acid biosynthesis, take part in the biosynthesis of alkaloids, glycosides and other biologically active compounds, and serve as a link between the individual stages of the metabolism of fats, proteins and carbohydrates. In addition LMWOAs involved in the pH regulation, maintaining of ion homeostasis in the cell and its osmotic potential (Sharma et al., 2016; Wang et al., 2019). At the same time, a number of organisms, including plants, bacteria and fungi, are able to excrete synthesized organic acids into environment (López-Bucio, 2000; Ryan et al., 2001; Yadav et al., 2022) while the prevalence and intensity of this phenomenon in fungi is incomparably higher (Magnuson, Lasure, 2004; Papagianni, 2007).

The first information about the production of organic acids by fungi dates back to the second half of the 19th century (Hamlet, Plowright, 1877; Zhuravsky, 1939). Most researchers at the beginning of the 20th century, before establishing the sequence of reactions of the tricarboxylic acid cycle (TCA cycle), assumed the closest relationship between the formation of citric, succinic, malic and fumaric acids with the process of sugar oxidation. The pathways for the biosynthesis of organic acids from carbohydrates were first described by Franzen, Schmitt, Challenger, Walker, and Subramaniam (Bennet-Clark, 1938). Later, it was noted that organic acids formed by fungi first accumulate in the nutrient solution and then disappear. This circumstance gave rise to the idea that acids are used as a source of nutrition when sugars are depleted in the nutrient medium. Those LMWOAs are intermediates in the oxidation of sugars to carbon dioxide (Butkevich, 1957).

At present, the pathways of organic acid metabolism are fairly well understood. There are many works about its regulation, especially great attention is paid to the hyperproduction of acids that are of biotechnological importance. However the specific functions of acids and the reasons for their hyperproduction in fungi are not always understood, and the available data are clearly not sufficient to explain this phenomenon.

Most often in the largest amount gluconic, citric, malic, fumaric, succinic and oxalic acids are produced by fungi (Max et al., 2010; Sazanova et al., 2015, 2016;

Show et al., 2015; Almousa et al., 2018). Obviously for fungi organic acids acquire a particularly important ecological and physiological significance, including in view of their changes in the surrounding micro-conditions and influencing biotic and abiotic relationships in the community. In the natural habitat, the production of organic acids has many ecological functions, which are discussed in detail in this review. At the same time, it is very labile process, depended on many factors, and at present there are only a few attempts to extrapolate the data obtained in vitro to the processes in nature.

The production of organic acids by fungi is of great importance for applied mycology and biotechnology. For industrial purposes fungal strains are used that are characterized by overproduction of organic acids when cultivated on artificially selected media. According to some data, *Aspergillus niger* Tiegh. is able to release citric acid up to 300 g/l of nutrient medium under culture conditions (Al-Sheri, Mostafa, 2006), although these amount are generally much lower. The ability to active citric acid excretion was the reason for *A. niger* usage for industrial acid production (Magnuson, Lasure, 2004; Papagianni, 2007; Pel et al., 2007; Andersen et al., 2011; Show et al., 2015; Almousa et al., 2018; Ozdal, Kurbanoglu, 2019).

On the other hand, organic acids produced by fungi are considered as one of the most important factors in the destruction of various building materials and structures, as well as of cultural heritage (Scheerer, 2009; Warscheid, Braams, 2000; Sterflinger, 2010; Gadd et al., 2014; Boniek et al., 2017).

There is also evidence of the role of fungal organic acids in the processes of pathogenesis in animals and humans. In pulmonary aspergillosis in humans, especially when affected by the fungus *A. niger* and, less commonly, *A. fumigatus* Fresen., calcium oxalate crystals form in the lungs. Calcium oxalates are localized in places of the greatest accumulation of mycelium. This phenomenon, called oxalosis, complicates the treatment of aspergillosis and is considered as one of its most dangerous consequences, in especially severe cases leading to the death (Muntz, 1999; Pabuççuolu et al., 2003; Roehrl et al., 2007). Similar phenomena have also been observed in veterinary medicine (Muntz, 1999).

Thus, research on organic acids production by fungi is important for understanding the many ecological and global geochemical processes involving fungi, and has of great practical importance for biotechnology, medicine, and cultural heritage conservation.

In this review we aimed to summarize data about the metabolism and excretion of organic acids by fungi and the functions of organic acids in biogeocenosis.

METABOLISM OF ORGANIC ACIDS

Gluconic acid

Gluconic acid is produced by fungi from D-glucose by the oxidation of its aldehyde group (C1) to a carboxyl group through a dehydrogenation reaction catalyzed by glucose oxidase (unlike glucuronic acid, where C6 is oxidized to a carboxyl group, and glucaric acid, where both C1 and C6 are carboxylic groups). Oxidation of the aldehyde group on the C-1 of beta-D-glucose to a carboxyl group results in the production of glucono-δ-lactone and hydrogen peroxide. Glucono-δ-lactone is further hydrolyzed to gluconic acid either spontaneously or by a lactone-hydrolyzing enzyme (Karaffa et al., 2021; Yadav et al., 2022).

Unlike other acids secreted by fungi, gluconic acid is a product synthesized mainly extracellularly. Depending on the fungal genera, glucose oxidase is either a fully extracellular enzyme or partially cell wall-bound. However, a gene encoding intracellular glucose oxidase was also found in *A. niger* (Pel et al., 2007). Glucose oxidase is a dimer of two identical subunits containing one FAD molecule each. FAD is restored during glucose oxidation. The subsequent oxidation of $FADH_2$ is accompanied by the formation of hydrogen peroxide, which is decomposed by catalase (Ramachandran et al., 2006).

Gluconic acid, formed by mycelium or added to the medium, is a substrate that is easily absorbed and metabolized by fungi and can be used by them as the sole carbon source (Elzainy et al., 1973; Müller, 1986; Elshafei, 1989). Two gluconate-specific kinases have been identified in *A. niger*, and it is assumed that gluconic acid catabolism occurs through its phosphorylation to 6-P-gluconate (Pel et al., 2007). Further 6-P-gluconate is included in the pentose phosphate pathway. In addition, gluconic acid can be metabolized in another way, not related to its phosphorylation, where it is dehydrogenated using the enzyme gluconate dehydrogenase, and the 2-keto-3-deoxygluconate formed as a result of this reaction is cleaved by 2-keto-3-deoxy gluconat aldolase into pyruvate and glyceraldehyde (Elzainy et al., 1973; Ramachandran et al., 2006).

The pathways of organic acids biosynthesis in fungi are illustrated on scheme (Fig. 1).

Citric, succinic, fumaric and malic acids

Oxidation of glucose via the glycolytic pathway leads to the formation of pyruvate. With sufficient oxygen, pyruvate is decarboxylated to acetyl-CoA by the mitochondrial pyruvate dehydrogenase complex. Acetyl-CoA then enters the TCA cycle and reacts with oxaloacetate to form citric acid (Peksel et al., 2002). The enzyme citrate synthase, which catalyzes this reaction, is inhibited by Mg^{2+} and ATP, but not by citric acid (Papagianni, 2007).

Another pathway of pyruvic acid metabolism in fungal cell is also possible. In the 1960s, the fixation of

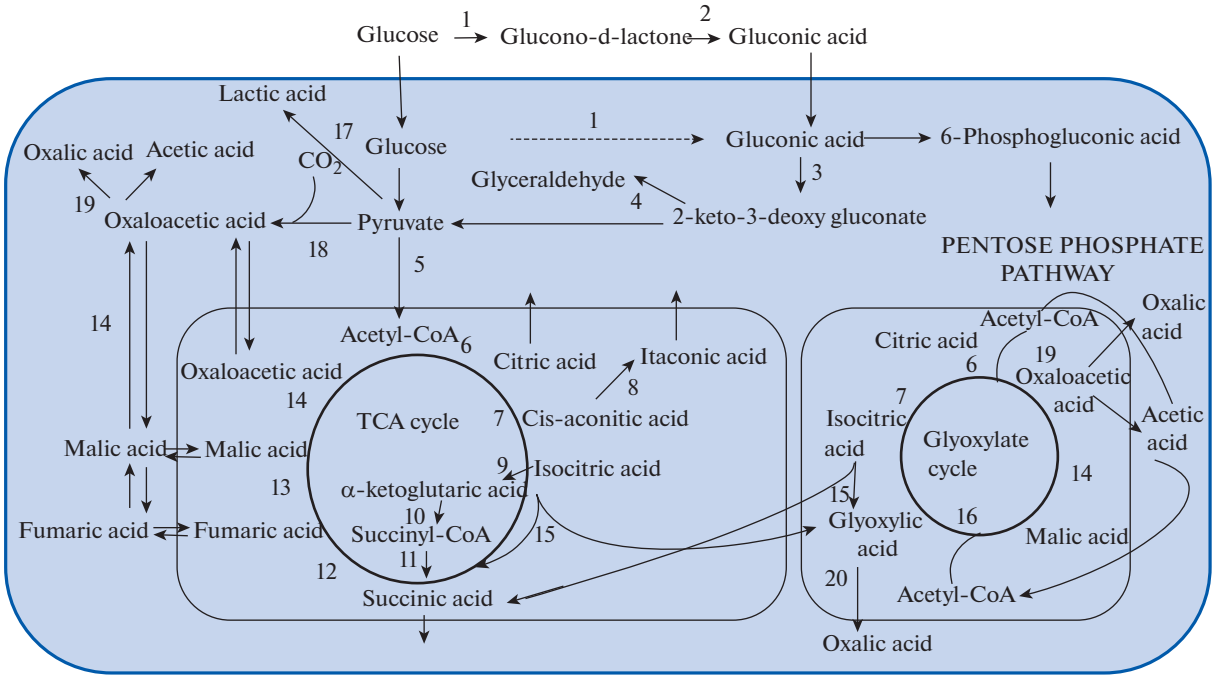

Fig. 1. The main pathways of organic acids metabolism in fungi: 1 – glucose oxidase; 2 – gluconolactonase; 3 – gluconate dehydrogenase; 4 – 2-keto-3-deoxy gluconat aldolase; 5 – pyruvate dehydrogenase; 6 – citrate synthase; 7 – aconitase; 8 – cis-aconitate decarboxylase; 9 – isocitrate dehydrogenase; 10 – oxoglutarate dehydrogenase; 11 – succinyl-CoA synthase; 12 – succinate dehydrogenase; 13 – fumarate hydratase; 14 – malate dehydrogenase; 15 – isocitrate lyase; 16 – malate synthase; 17 – lactate dehydrogenase; 18 – pyruvate carboxylase; 19 – oxaloacetate acetylhydrolase; 20 – glyoxylate dehydrogenase.

CO_2 in fungi by pyruvate carboxylase with the formation of oxaloacetic acid was proposed (Woronick, Johnson, 1960; Bloom, Johnson, 1962). Later one mitochondrial and one cytoplasmic pyruvate carboxylase were found in *A. niger* (Pel et al., 2007). The resulting oxaloacetic acid, in the case of its synthesis in the cytoplasm, can be transported to mitochondria (through the oxaloacetate translocator in exchange for malate) and included in the TCA cycle. In addition, oxaloacetate can be converted to malic acid by cytoplasmic or mitochondrial malate dehydrogenase (Ma et al., 1981; Pel et al., 2007).

The citric acid formed during the citrate synthase reaction undergoes an isomerization reaction to isocitrate under the aconitase. The cis- aconitic acid formed during this reaction can be decarboxylated by cis-aconitate decarboxylase to form itaconic acid (Bonnarme et al., 1995; Willke, Vorlop, 2001; Magnuson, Lasure, 2004; Pel et al., 2007). Isocitric acid is decarboxylated to α-ketoglutarate by NAD-dependent isocitrate dehydrogenase and undergoes oxidative decarboxylation by oxoglutarate dehydrogenase to form succinyl-CoA. The conversion of succinyl-CoA to succinic acid is catalyzed by the enzyme succinyl-CoA synthase and is accompanied by the formation of ATP. In addition to the oxidation of α-ketoglutarate, the formation of succinic acid is possible by reduction of fumaric acid by succinate dehydrogenase and from isocitrate during the glyoxylate pathway (Munir et al., 2001; Magnuson, Lasure, 2004).

The oxidation of succinic acid to fumaric acid is carried out with the participation of succinate dehydrogenase. A cytoplasmic pathway for the synthesis of fumaric acid from malic acid is also possible due to fumarate hydratase (fumarase) in the cytoplasm. Moreover, in the case of intensive production of fumaric acid by the organism, its activity is high (Carol et al., 2008).

The malic acid, as well as fumaric acid, can be form in mitochondria or in cytoplasm. In the TCA cycle, fumaric acid, under fumarase enzyme, adds water that leads to malic acid formation. Further, malic acid is oxidized by the enzyme malate dehydrogenase to oxaloacetic acid with the formation of NADH (Peksel et al., 2002). Fungi are thought to have three cytoplasmic and one mitochondrial malate dehydrogenases (Pel et al., 2007). Cytoplasmic malate dehydrogenase generates malic acid from oxaloacetic acid synthesized as a result of CO_2 fixation by cytoplasmic pyruvate carboxylase (Ma et al., 1981; Magnuson, Lasure, 2004). Further, malate formed in the cytoplasm can be transported to mitochondria, oxidized to oxaloacetate, and condensed with acetyl-CoA to form citric acid (Papagianni, 2007).

Isocitrate lyase catalyzes the reversible cleavage of isocitrate into succinate and glyoxylate and supplies glyoxylate and succinate to the glyoxylate and tricarboxylic acid cycles, respectively. Further, glyoxylate is

condensed with acetyl-CoA by malate synthase to form malate, a precursor of oxaloacetate (Munir et al., 2005).

It is assumed that the excretion of di- and tricarboxylic acids occurs with the participation of transport proteins (Gallmetzer et al., 1998; Gallmetzer, Burgstaller, 2002). Odoni et al. (2019) were able to identify a gene encoding the transport protein of citrate transporter in gene encoding the transport protein of citrate transporter in *A. niger*, but no citrate exporters have yet been identified. It is known the transport systems of malic and succinic acids in most fungi are inhibited by glucose (Jennings, 2007).

With a lack of carbohydrates in the nutrient medium, gluconic, malic, citric, succinic and fumaric acids are consumed by mycelium (Côrte-Real, Leao, 1990; Ghorbani et al., 2007; Sazanova et al., 2016). In this case, the formation of oxalic acid is sometimes observed (Gadd, 1999; Sazanova et al., 2016).

Lactic acid

In case of a lack of oxygen in the cytosol, lactic acid is biosynthesized from pyruvic acid using the enzyme lactate dehydrogenase (Magnuson, Lasure, 2004; Zhang et al., 2007). In *Rhizopus oryzae* Went et Prins. Geerl., three isoforms of lactate dehydrogenase have been identified: two NAD-dependent and one NAD-independent (Yu, Hang, 1991; Skory, 2000). Molecular studies with gene-specific primers have shown that the two NAD-dependent lactate dehydrogenase genes are differentially expressed. The *ldn* A gene is expressed in the presence of glucose, xylose, and trehalose. The *ldn B* gene is expressed only in the presence of ethanol, lactate, and non-fermentable carbon sources. It is assumed that *ldn* A encodes lactate dehydrogenase, which carries out the reductive reaction pyruvate → lactate, while *ldn* B encodes lactate dehydrogenase, which catalyzes the oxidative reaction lactate → pyruvate (Magnuson, Lasure, 2004).

Oxalic acid

The mechanism for the formation of oxalic acid from oxaloacetate in *Aspergillus niger* was first proposed in 1956 by Hayashi et al. (1956). They associated the formation of this acid with the activity of the enzyme oxaloacetate acetylhydrolase (oxaloacetase) (Hayaishi et al., 1956). Since inhibition of TCA cycle in mitochondria did not cause a decrease in the formation of oxalic acid, an assumption was made about the cytoplasmic localization of oxaloacetase. This was later confirmed by fractionation of *A. niger* mycelial cells (Kubicek et al., 1988).

Hydrolysis of oxaloacetic acid by the cytoplasmic oxaloacetate acetylhydrolase was subsequently recognized as the main pathway for the synthesis of oxalic acid by fungi (Munir et al., 2001; Magnuson, Lasure, 2004; Pel et al., 2007). In addition to *A. niger*, oxaloacetase activity was found in *Sclerotinia sclerotiorum* (Lib.) de Bary, *Cryphonectria parasitica* (Murrill) M.E. Barr, *Tyromyces palustris* (Berk. et M.A. Curtis) Murrill, *Trametes versicolor* (L.) Lloyd, and *Phanerochaete chrysosporium* Burds. (Dutton, Evans, 1996). Subsequent studies showed that oxaloacetase-deficient *A. niger* strains did not produce oxalic acid (Ruijter et al., 1999). Experiments by Pedersen et al. (2000) and Han et al. (2007) demonstrated that disruption of the *oah* gene encoding oxaloacetase in *A. niger* and *Botrytis cinerea* Pers. leads to the formation of oxalic acid-incapable mutants. As a result, it was suggested that the presence of this gene in fungi is necessary for biosynthesis of oxalate (Pedersen et al., 2000; Han et al., 2007). This oxalic acid biosynthetic pathway does not produce ATP (pyruvate carboxylase requires 1 ATP to form oxaloacetate). The activity of oxaloacetase requires neutralization of the resulting acids and the presence of carbonate in the medium (Kubicek et al., 1988; Gadd, 1999; Pedersen et al., 2000), as well as Mn^{2+} (Hayaishi et al., 1956; Lenz et al., 1976; Gadd, 1999; Ruijter et al., 1999). Oxaloacetase activity is inhibited by oxalic (Ruijter et al., 1999) and malic acids (Han et al., 2007). Acetate is not an oxaloacetase inhibitor (Ruijter et al., 1999).

As regards the formation of the precursor of oxalic acid, oxaloacetate, its formation in the cytoplasm from pyruvic acid was shown in *A. niger*, to occur due to the enzyme pyruvate carboxylase (Kubicek et al., 1988). Later it was shown that in wood-destroying fungi, the main part of oxaloacetate is formed by the oxidation of malic acid by malate dehydrogenase (Munir et al., 2001). The acetic acid formed during the hydrolysis of oxaloacetate can be included in the formation of acetyl-CoA and then enter the glyoxylate cycle.

An alternative pathway for the biosynthesis of oxalic acid is its formation from glyoxylic acid with the participation of the enzyme glyoxylate dehydrogenase (Pel et al., 2007; Munir et al., 2001, 2005), although oxaloacetase, apparently, still has a much more contribution (Dutton, Evants, 1996; Munir et al., 2001).

The biochemical role of oxalic acid biosynthesis primarily consists in the oxidation of acetyl-CoA with the formation of oxalate, which accumulates in the culture liquid as the final product. The oxidation of malate to oxaloacetate, the precursor of oxalate, is accompanied by the formation of NADH. The formation of oxalate is thus an energetically favorable process (Munir et al., 2001).

The transport of oxalic acid through the plasmalemma has been studied in detail in *Fomitopsis palustris* (Berk. et M.A. Curtis) Gilb. et Ryvarden. The results of these studies have shown that active oxalate transport requires Mg and ATP. Vanadate, an inhibitor of P-type ATPases and ABC transporters, significantly reduced the transport of oxalate across the membrane (by 68%). The addition of valinomycin or NH_4Cl, which prevent the formation of $\Delta\psi$ and ΔpH, inhibited oxalate transport by 86 and 90%, respectively. Inhibitors of ABC

transporters, glibenclamide and cyclosporine, did not affect oxalate transport. Thus, it was concluded that secondary oxalate transport occurs in *F. palustris*, which requires the creation of $\Delta\psi$ and ΔpH, while ABC transporters do not perform the leading function in oxalic acid transport (Watanabe et al., 2010).

Unlike most other acids produced by fungi, oxalic acid is not consumed by the mycelium as a nutrient substrate (Espejo, Agsin, 1991). However, fungi have enzyme systems capable of degrading oxalate. The first system includes the oxidation of oxalate by oxalate oxidase with the formation of two CO_2 molecules and one H_2O_2 molecule. This system has been well studied in plants, while in fungi it has been discovered relatively recently and has been shown only in a few species (Dutton, Evants, 1996; Makela et al., 2009; Grąz et al., 2016).

The second system, more common in fungi, involves the decarboxylation of oxalic acid by oxalate decarboxylase to form formic acid and CO_2 (Dutton, Evants, 1996; Pel et al., 2007; Makela et al., 2009; Hastrup et al., 2012). It is believed that oxalate decarboxylase is localized mainly inside the mycelium, near the plasma membrane and intracellular vesicles. In the culture liquid of fungi, the cell wall, and in the extracellular polysaccharide layer, its activity is very low (Dutton et al., 1994; Kathiara et al., 2000; Makela et al., 2009). According to other data, in the wood-decay fungus *Postia placenta* (Fr.) M.J. Larsen et Lombard, the greatest amount of oxalate decarboxylase was observed precisely on the surface of the hyphae of the fungus, while the activity of the enzyme was lower in the extract from the mycelium and in the cultural liquid (Micales, 1997).

Oxalate decarboxylase is a Mn^{2+} containing enzyme (Makela et al., 2009). The pH optimum for this enzyme is 3.6 and the temperature optimum is 35°C (Kathiara et al., 2000). Under culture conditions, the formation of oxalic acid occurs during the stationary phase, when the pH of the medium is predominantly in the alkaline region, the enzyme activity is suppressed under these conditions, and oxalate decarboxylation occurs weakly. A similar phenomenon is also observed when calcium carbonate is added to the medium (Dutton, Evants, 1996).

It is assumed that the main role of fungal oxalate decarboxylase is to prevent the accumulation of too large amounts of oxalic acid (Micales, 1997; Makela et al., 2009). Oxalate decarboxylase released into the medium degrades extracellular oxalic acid to maintain a certain pH level and oxalate anions outside the cell (Dutton et al., 1994; Micales, 1997; Makela et al., 2009; Schilling, Jellison, 2005).

Oxalate decarboxylase activity is well known for white rot fungi (Makela et al., 2009). Brown rot fungi usually accumulate oxalate in the culture medium and it was assumed that the higher accumulation of oxalic acid observed in brown-rot fungi compared to white-rot fungi is explained by the inability of the former to undertake active regulation of this organic acid (Akamatsu et al., 1992). However, there is evidence that the brown-rot fungi, and in particular *Gloeophyllum trabeum* (Pers.) Murrill, are capable of regulating oxalic acid concentration during wood decay by decarboxylation (Hastrup et al., 2012).

Schilling and Jellison (2005) demonstrated that brown rot fungi can regulate wood oxalate and pH during decay, but this regulation may be dependent on the environment of decay. The authors could not fully explain the reason for the decrease in the content of oxalates in wood during decay, but the role of the brown rot fungi *Meruliporia incrassata* (Berk. et M.A. Curtis) Murrill and *Fomitopsis pinicola* (Sw.) P. Karst. in this process is evident. There is an assumption that the formation of calcium oxalate crystals by brown-rot fungi may neutralize the oxalic acid at the hyphal surface and substitute the need for oxalate-catabolizing enzymes such as oxalate decarboxylase (Micales, 1995).

REGULATION OF BIOSYNTHESIS AND PRODUCTION OF ORGANIC ACIDS BY FUNGI

The intensity of excretion and the quantitative ratio of the organic acids produced by fungi varies significantly depending on growth conditions.

Carbone source

It is believed that the best carbon sources for the production of acids by fungi are mono- and disaccharides, primarily glucose and sucrose (Hossain et al., 1984; Xu et al., 1989; Singh et al., 2001; Papagianni, 2007). The productivity of the formation of oxalic acid by *A. niger* does not significantly change when glucose, fructose, sucrose, gluconate, xylose, acetate, and glycerol are used as a carbon source (Ruijter et al., 1999). It is known that fungi can synthesize organic acids in significant amounts using other substances. Some strains of *A. niger* produce oxalic and citric acids at concentrations up to 54 g/l and 36 g/l, respectively, using petroleum as a carbon source (Rymowicz, Lenart, 2002).

According Dörsam et al. (2017), *Aspergillus oryzae* (Ahlb.) Cohn is able to convert into organic acids a number of sugars including levoglucosan, glucose, galactose, mannose, arabinose, xylose, ribose, cellobiose, fructose, and maltose to malate, albeit in varying yields.

Gluconic acid is produced in greatest quantities using glucose (Singh et al., 2001), although there is evidence that gluconic acid is often formed by fungi using other carbon sources (Ramachandran et al., 2006).

In most cases, the formation of acids by fungi increases with an increase in the concentration of carbohydrates in the medium (Braams, 1992; Gallmetzer, Burgstaller, 2002; Rosling et al., 2004; Magnuson, La-

sure, 2004; Al-Shehri, Mostafa, 2006). According to some data, at a sugar concentration of less than 2.5%, the formation of citric acid does not occur (Xu et al., 1989). Our previous study shown that oxalic acid was produced by fungi grown on media with various concentrations of sugars, sugar alcohols, and organic acids. Malic, citric, fumaric, and succinic acids were identified only at elevated carbohydrate concentrations (more than 3%), mostly in liquid cultures. That an increasing concentration of carbohydrates in the medium contributed to the release of acids, which are formed mainly in the TCA cycle and, unlike oxalic acid, are not metabolic end products, but intermediates that can be included in further physiological reactions (Sazanova et al., 2014, 2016). One of the possible mechanisms contributing to the release of these organic acids from the cell in fungi, may be "catabolic inactivation", i.e. inhibition by sugars in a high concentration of the expression of genes of some respiratory enzymes (Flavell, 1970; Blank, Sauer, 2004; Portnoy, 2011).

In a study by Brunner et al. (2014) it was shown that carbohydrate sources, which contain not only C but also nutrient elements, e.g., algal substrates or pollen material, can trigger better the exudation of organic acids compared to pure and simple carbohydrates such as glucose. Thus, the occurrence of complex carbohydrate sources in nutrient-deficient deglaciated soils may positively influence the exudation of organic acids of fungi.

Nitrogen source

Too low or high concentrations of nitrogen lead to a violation of the growth and development of fungi, as well as reducing acid production. The maximum amount of citric acid in *A. niger* was obtained at a concentration of about 0.2% NH_4NO_3 in a medium. Nitrogen deficiency, on the other hand, may promote the oxidation of glucose to gluconic acid by some fungi (Ali et al., 2002a).

In plants, more intensive formation of organic acids (succinate, malate, citrate, fumarate) occurs under conditions of assimilation of predominantly nitrate nitrogen, rather than ammonium nitrogen (Lambers et al., 2008). In fungi, as a rule, a similar dependence is observed. Using the mycorrhizal fungus *Paxillus involutus* (Batsch) Fr. as an example, it was shown that when using nitrate as a source of nitrogen, a greater release of oxalic acid is observed than when using ammonium (Dutton, Evants, 1996). Although in other studies conducted on *A. niger*, the use of different nitrogen sources ($NaNO_3$ and NH_4Cl) and changing their concentrations from 6 to 50 mmol had almost no effect on the amount of oxalic acid secreted by mycelium (Ruijter et al., 1999).

In addition to the direct influence of nitrogen sources on the growth and formation of acids by fungi, the ratio of carbon and nitrogen in the environment is also important. A high C/N ratio is favorable for the excretion of acids – products of the TCA cycle (Gallmetzer, Burgstaller, 2002; Magnuson, Lasure, 2004; Carol, 2008; Sazanova et al., 2016).

Metal ions

In addition to an excessive level of carbon source, an optimal source of nitrogen, sufficient aeration, the production of organic acids is also dependent on certain trace elements that synergistically affect their production. Their common role in fungal physiology is to provide redox and catalytic activity for a variety of important biochemical reactions as cofactors for enzymes that directly or indirectly affect the biosynthesis of organic acids. Particularly emphasize the importance of five metals Zn, Mn, Mg, Fe, и Cu (Ali et al., 2002b; Papagianni, 2007; Karaffa et al., 2021). Thus, manipulating the supply of cofactors by carefully adjusting the concentration of these metals can fundamentally change the distribution of fluxes in the cell, causing metabolic overload.

The lack of Fe ions, a cofactor of aconitase, increases the formation of citric acid by blocking the subsequent reaction of its transformation in the TCA cycle (Braams, 1992; Carlile et al., 2001). An increase in the concentration of Cu in the medium has a stimulating effect on the synthesis of oxalic, citric and some other acids by fungi (Ramsay et al., 1999; Gibson, Mitchell, 2004; Fomina et al., 2005; Munir et al., 2005; Betlej, Grąz, 2006). Zn causes an increase in the synthesis of citric acid, and also promotes the synthesis of malic acid (Fomina et al., 2005). Mg has a stimulating effect on the synthesis of oxalic acid, since it is necessary for the functioning of oxaloacetase (Hayaishi et al., 1956; Lenz et al., 1976). In addition, Mn activates isocitrate dehydrogenase (Williams, Pittman, 2010).

The action of metals may vary for different fungi. The addition of Mg to the medium at concentrations of 1×10^{-6}–4×10^{-6} leads to an increase in the production of citric acid in some strains and a decrease in its production in others (Ali et al., 2002b). In addition, the influence of elements can manifest itself differently even at the species level, depending on the growth conditions. For example, on nitrate media, zinc stimulates the formation of oxalic acid in *Aspergillus niger* and *Penicillium citrinum* Thom, while on ammonium media, it practically does not affect the production of organic acids (Sazanova et al., 2015).

An increase in the concentration of some potentially toxic metals (Cd, Ni, Pb) in the medium stimulates the synthesis of oxalic, citric, malic, and some other acids by fungi (Dutton, Evans, 1996; Ramsay et al., 1999; Gibson, Mitchell, 2004; Fomina et al., 2005), which seems to be a response to stress.

Acidity

The ratio of organic acids secreted by fungi largely depends on the acidity of the medium. Low acidity

promotes the accumulation mainly of oxalic (Ruijter et al., 1999; Carlile et al., 2001; Ali et al., 2002a; Al-Shehri, Mostafa, 2006) and gluconic acids (Braams, 1992). Optimal for the biosynthesis of gluconic acid is pH 6.5. At a nutrient solution pH of less than 3.5, the work of the glucose oxidase enzyme is completely inactivated (Anastassiadis, Rehm, 2006). The acidity of the extracellular solution is one of the main regulators of oxaloacetase activity. The activity of this enzyme is suppressed by low pH (Kubicek et al., 1988; Ruijter et al., 1999). It is believed that high acidity induces the formation of citric acid (Carlile et al., 2001; Zhang, Röhr, 2002a, 2002b). It is possible that the formation of citrate is enhanced at high acidity of the medium due to a decrease in carbon consumption for the formation of oxalic and gluconic acids (Ruijter et al., 1999). *A. niger* mutants lacking glucose oxidase (*gox C*) and oxaloacetase (*prt F*) produced citric acid in large amounts and at neutral pH. The most intensive formation of lactic and fumaric acids of *Rhizopus* sp. observed at pH 6.0–6.5 and decreases with increasing acidity (Zhang et al., 2007).

Temperature

The temperature optimum for the formation of most acids is 25–30°C (Ali et al., 2002a; Haq et al., 2002; Al-Sheri, Mostafa, 2006; Anastassiadis, Rehm, 2006; Zhang et al., 2007). At extremely high temperatures at 40°C, the biosynthesis of oxalic acid is activated, while the formation of citric and some other acids is suppressed (Haq et al., 2002).

UV irradiation

In most cases the metabolic response of fungi to stressful exposure under UV light is to increase the production of citric acid by fungi (Vasanthabharathi et al., 2013), although in some strains exposed to long-term exposure to UV radiation, the production of citric acid is reduced (Tembhurkar et al., 2012). In cultures of micromycetes *Aspergillus niger*, *Rhodotorula colostri* (T. Castelli) Lodder, and *Geomyces pannorum* (Link) Sigler et J.W. Carmich. irradiated by UV light, the intensity of oxalic acid production increased. Unlike *Aspergillus niger* and *Rhodotorula colostri*, *Geomyces pannorum* also increased the production of succinic, fumaric, and malic acids under UV influence (Sazanova et al., 2014).

UV along with chemical mutagens (for example, sodium azide, ethidium bromide, aziridine, N-nitroso-N-methylurea, ethyl methanesulfonate), is used to select strains that are hyperproducers of organic acids (Musilkova et al., 1983; Tembhurkar et al., 2012). In mutant strains obtained by prolonged exposure to UV light, gluconic acid biosynthesis is stimulated due to the activation of the glucose oxidase enzyme (Prabu et al., 2012). Strains of *Apergillus niger* – hyperproducers of citric acid have mutations in the genes associated with plasma membrane ATPase, the TCA cycle, and in the components of the electron transport chain (Andersen et al., 2011). An increase in the biosynthesis of acids-intermediates of the TCA cycle was also observed in plants exposed to UV irradiation (Kim et al., 2012).

ECOLOGICAL ROLE OF FUNGAL ACID PRODUCTION

Role of organic acids in wood decay

Wood-decaying fungi, especially brown rot, produce oxalic acid in large quantities (Espejo, Agosin, 1991; Dutton et al., 1993; Munir et al., 2005; Makela et al., 2009; Jarosz-Wilkołazka, Grąz, 2006).

In brown rot fungi, the formation of oxalic acid is most likely associated with its function of reducing Fe (III) to Fe (II) and its subsequent participation in the depolymerization of wood cellulose due to participation in Fenton reactions (Espejo, Agosin, 1991). Oxalic acid produced by brown rot fungi plays an important role in the Fenton reaction due to its ability to bind and dissolve iron from Fe oxyhydroxide complexes in the wood lumen region. Conditions of pH can strongly influence the dissolution of iron oxides (Arantes et al., 2012).

In white rot fungi, oxalate and malonate, in lesser degree promote the work of manganese peroxidases that are part of the ligninolytic system (Dutton et al., 1993; Kuan, Tien, 1993; Dutton, Evants, 1996; Çaliskan, 2000; Munir et al., 2005). During the catalytic cycle, the active center is oxidized by H_2O_2. Reduction to the resting enzyme is achieved by two consecutive one-electron transfers, as a result of which Mn^{2+} is oxidized to Mn^{3+}, respectively. This is promoted by action of organic acids during chelation of the highly reactive Mn^{3+} state (Schlosser, Höfer, 2002).

Organic acid – a virulence factor for pathogenic fungi

The secretion of organic acids is important during the fungal invasion and pathogenesis process, since the environmental pH effectively regulates the growth and development of fungi, promotes the penetration of hyphae into plant tissues, and also increases their virulence and pathogenicity (Prusky et al., 2008). Organic acid molecules secreted by acidic fungi are multifunctional, including activating virulence factors and enhancing the pathogenicity of certain fungi (Jiao et al., 2022).

Penicillium spp. mainly secrete gluconic and citric acids (Prusky et al., 2004; Hadas et al., 2007). For phytopathogenic fungi *Sclerotium rolfsii* Sacc., *Sclerotinia sclerotiorum*, *Rhizoctonia solani* J.G. Kühn, and *Botrytis cinerea*, oxalic acid is one of the key pathogenic factors (Cessna et al., 2000; Rollins, Dickman, 2001; Manteru et al., 2003; Prusky, Lichter, 2008). There is evidence that the intensity of organic acid biosynthesis correlates with the pathogenicity and virulence of phy-

topathogenic fungi (Kunz et al., 2006; Barad et al., 2012; Liang et al., 2015). For example, the transcription factor (*pacC*) mutant of *Aspergillus carbonarius* (Bainier) Thom is unable to effectively acidify the nutrient medium or infect its host as a result of reduced production of gluconic and citric acids (Barda et al., 2020).

The main role of organic acids in the process of pathogenesis is associated with acidification of the environment. Generally, an acidic pH is optimal for extracellular cell wall degrading enzymes such as cellulase, hemicellulase and pectinase produced by phytopathogenic fungi (Prusky et al., 2004; Hadas et al., 2007). In addition, the toxic effect of oxalic acid itself leads to tissue damage and plant cell death (Magro et al., 1984; Verhoeff et al., 1988; Pinna, 1993; Dutton, Evants, 1996). Oxalic acid inhibits polyphenol oxidase activity in plants and also induces the formation of reactive oxygen species (Xiao-ting et al., 2009) and intensifies programmed cell death in plants (Williams et al., 2011). In addition, oxalic acid inhibits early defense responses in the host plant (Cessna et al., 2000; Williams et al., 2011).

Oxalic acid binding of Ca^{2+} ions in the plant cell wall can also facilitate the penetration of fungi into plant tissues (Pinna, 1993; Dutton, Evants, 1996; Hadas et al., 2007). Oxalic acid chelates Ca^{2+} to form insoluble calcium oxalate crystals that erode cell walls causing host plant wilt (Cessna et al., 2000; Prusky, Lichter, 2008).

Chelation of Ca^{2+} by citric acid is also to impair host cell wall function and lead to cell death. The accumulation of citric acid reduces Ca^{2+} activity between plant cells, changing the mineral balance and affecting the stability of cell membranes and cell wall pectin polymers (Jiao et al., 2022).

The role of organic acids in the formation of mycorrhiza

The production of organic acids is also a common feature of many ectomycorrhizal fungi (Malajczuk, Cromack, 1982; Dutton, Evants, 1996; Rosling et al., 2004; Kanwal, 2006). It is believed that the oxalic acid secreted by them is essential in the formation of mycorrhiza, contributing to the trophic connection between the root and hyphae of fungi (Malajczuk, Cromack, 1982; Dutton, Evants, 1996). In some cases, the predominant acids secreted by ectomycorrhizal fungi are citrate and malate (Nowotny et al., 1998; Blaudez et al., 2000). It is assumed that the release of oxalic acid by the mycorrhizal fungus *Paxillus involutus* has a toxic effect on pathogenic fungi in the rhizosphere, thus contributing to the protection of the roots of *Pinus* sp. It has also been noted that pine root exudates stimulate the production of oxalic acid by *P. involutus* (Allen et al., 1992).

The role of organic acids in geochemical cycles

Organic acids exudation by fungi play a major role in mineral weathering contributing to the geochemical carbon cycle. The acidification ability largely determines the geochemical role of fungi and their importance in rock weathering and primary soil formation processes (Ferris et al., 1994; Vaughan et al., 2002). Organic acids play an important role in changing the solubility of compounds (Nowotny et al., 1998; Wallander, Wickman, 1999; Blaudez et al., 2000; Rosling et al., 2004; Kanwal, 2006). Acidification of the environment promotes the extraction of elements such as P, K, Al, Fe from minerals, and the transfer of some of them into forms more accessible to organisms (Hoffland et al., 1992; Jones, Darrah, 1995; Ohwaki et al., 1997; Ghorbani et al., 2007; Posso et al., 2017). It is well known that acids secreted by plant roots can have a similar effect (López-Bucio, 2000).

The secretion of oxalic acid is believed to play a major role in the dissolution of apatite, the release of phosphorus for uptake by ectomycorrhizal fungi, and the immobilization of the released calcium into calcium oxalate (Smits et al., 2012).

The primary mechanisms of organic acid interaction with metals include acidolysis, complexolysis, bioaccumulation, and chelate formation (Blaudez et al., 2001; Rosling et al., 2004; Kanwal, 2006; Dusengemungu et al., 2021).

An intense release of oxalic acid is often observed in fungi living on substrates with a high Ca^{2+} content (Dutton, Evans, 1996; Cezar, 1998; Adamo, Violante, 2000; Kolo, Claeys, 2005). Fungi, as well as plants growing in alkaline soils rich in calcium, can use organic acids to bind excess calcium. Calcium chelation is critical for survival in soils with high calcium concentrations that disrupt several cell metabolic processes such as calcium-dependent signaling, phosphorus metabolism, and cytoskeletal organization (Dutton, Evans, 1996; Adamo, Violante, 2000; López-Bucio, 2000).

Oxalic acid production by fungi is a powerful factor in modern mineral formation. Abundant formation of calcium oxalate crystals can be observed in fungal cultures (Monte, 2003; Gadd et al., 2014; Sturm et al., 2015). Oxalic acid forms insoluble salts with other divalent and trivalent metals. Zn, Cu, Fe and Pb oxalates were obtained in experimental controlled conditions under the influence of *Aspergillus niger* (Vlasov et al., 2020) as well as some other species (Fomina et al., 2005). However, most often and in the largest quantity, fungi form calcium oxalate. In the case of ectomycorrhizal fungi, it has been shown, the main chemical sink for secreted oxalate is the formation of crystaline calcium oxalate, irrespective of the chemistry of the minerals (Schmalenberger et al., 2015).

The role of organic acids in adaptation to heavy metals

Despite the fact that oxalates of potentially toxic heavy metals such as Fe, Zn, Pb, Cu, Cd, Ni and some others are formed by fungi much less frequently than calcium oxalates, among the mechanisms that ensure the resistance of fungi to heavy metals, an important role belongs to the extracellular chelation of metal ions by secreted acids (Gadd, 1993; Dutton, Evans, 1996; Gadd, 1999; Ramsay et al., 1999; Gibson, Mitchell, 2004; Fomina et al., 2005; Munir et al., 2005). The formation of complexes of organic acids with Al, Fe, Mg, Mn, Zn, Pb, Cu reduces the activity and toxicity of these metals in the soil or on another substrate and promotes the survival of fungi, as well as other organisms in an environment with their high content (Dutton, Evans, 1996; Gadd, 1999; Ramsay et al., 1999; Ruijter et al., 1999; Hoffland et al., 2004; Gibson, Mitchell, 2004; Fomina et al., 2005; Munir et al., 2005; Kanwal, 2006). The production of oxalic acid, which forms stable complexes and/or insoluble salts with a number of metals, is considered as a highly efficient method for the immobilization of toxic metals (Munir et al., 2005; Jenkins et al., 2012). In association with plants, the production of organic acids by fungi contributes to the resistance of plants to the heavy metals (Ahonen-Jonnarth, 2000).

CONCLUSION

The metabolism and excretion of organic acids by fungi is a very labile process which depends on many factors. Nutrient sources and the mineral composition of the substrate are the key importance. Increased production of organic acids by fungi is often a response to stress including heat, ultraviolet, and heavy metals. In nature, the production of organic acids by fungi favors for their assimilation of various substrates. Organic acids are involved in the formation of mycorrhiza, the processes of plant pathogenesis, and are also one of the key factors in wood decay. By changing the bioavailability of elements and the solubility of minerals, organic acids produced by fungi are very significant for the functioning of ecosystems.

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Продукция органических кислот грибами: метаболизм, физиологическая и экологическая значимость

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Обобщены и проанализированы данные о путях биосинтеза, регуляции метаболизма, физиологических и экологических функциях продукции органических кислот грибами различных экологических групп. Метаболизм и выделение органических кислот грибами зависят от многих факторов, в том числе от трофических условий, факторов минерального питания, температуры и различных стрессовых воздействий. Увеличение экскреции грибами органических кислот, особенно щавелевой кислоты, часто является реакцией на стресс. Продукция органических кислот имеет важное эколого-физиологическое значение, так как связана с изменением микроусловий окружающей среды и влиянием на биотические и абиотические взаимодействия микроорганизмов в сообществе. Органические кислоты участвуют в образовании микоризы, процессах патогенеза растений, а также являются одним из ключевых факторов гниения древесины. Способность к ацидофикации во многом определяет геохимическую роль грибов и их значение в выветривании горных пород и процессах первичного почвообразования.

Ключевые слова: макромицеты, метаболизм, микромицеты, органические кислоты, стресс, трофические условия, тяжелые металлы