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ANTIOXIDANT SYSTEMS AND OXIDATIVE STRESS RESPONSE IN FUNGI: BIOACTIVE METABOLITES WITH ANTIOXIDANT ACTIVITY

CEBOTARI D.[1] ORCID: 0009-0005-1955-1261
SARDARI Veronica[1] ORCID: 0000-0002-1047-9145
GRUȘAC E.[1] ORCID: 0009-0005-0719-3882
CRISTEA D.[1] ORCID: 0009-0005-0613-3933
RAILEAN Nadejda[2] ORCID: 0000-0001-7818-9200
GARBUZ Olga[2] ORCID: 0000-0001-8783-892X
[1] Department of Biochemistry and Clinical Biochemistry, Nicolae Testemițanu State University of Medicine and Pharmacy, Chișinău, Republic of Moldova
[2] Laboratory of Systematics and Molecular Phylogeny, Institute of Zoology, Moldova State University, Chișinău, Republic of Moldova
e-mail: cebotaridionisie@gmail.com

Abstract: Fungi are continuously exposed to reactive oxygen species (ROS) generated both by their own metabolism and by environmental and host-derived stress. To preserve redox homeostasis, they rely on a layered antioxidant network that combines enzymatic systems — superoxide dismutases, catalases, glutathione peroxidases, peroxiredoxins and the thioredoxin system — with low-molecular-weight and metabolite antioxidants such as glutathione, ergothioneine, melanins, phenolic compounds and polysaccharides. This response is coordinated mainly at the transcriptional level through activator protein 1 (AP-1)-like regulators (Yap1 and its orthologues), which sense oxidation and induce protective genes. Beyond their physiological role, many of these fungal metabolites display marked antioxidant activity *in vitro*, making macro- and micromycetes — particularly medicinal and wild edible mushrooms — a valuable and renewable source of natural antioxidants. The present review summarizes the main enzymatic and non-enzymatic antioxidant systems of fungi, the regulation of the oxidative stress response, and the diversity and applied potential of fungal antioxidant metabolites, underlining the relevance of conserving fungal biodiversity as a reservoir of bioactive compounds.

Keywords: oxidative stress; reactive oxygen species; antioxidant systems; fungi; ergothioneine; melanin; mushroom polysaccharides.

INTRODUCTION

Reactive oxygen species (ROS) — including the superoxide anion, hydrogen peroxide and the hydroxyl radical — are unavoidable by-products of aerobic metabolism and are further generated when fungi are challenged by environmental fluctuations, competing organisms, antifungal compounds or, in pathogenic species, the oxidative burst of the host [1, p. 333]. At low, controlled concentrations ROS act as signaling molecules that regulate growth, differentiation and development; when they accumulate, however, they damage lipids, proteins and nucleic acids, causing oxidative stress and, ultimately, cell death [1, p. 333; 2, p. 235–250]. To preserve this balance, fungi possess a complex and tightly regulated antioxidant network. It combines enzymatic components — superoxide dismutases, catalases, glutathione peroxidases, peroxiredoxins and the thioredoxin and glutathione systems — with low-molecular-weight and metabolite antioxidants, and it is controlled at the transcriptional level by dedicated stress-responsive regulators [2, p. 235–250]. Importantly, the fungal oxidative stress response is closely interconnected with secondary metabolism, so that the conditions which trigger antioxidant defenses also modulate the production of bioactive metabolites [3, p. 295–308]. Beyond their physiological role, many fungal metabolites — phenolic compounds, polysaccharides, ergothioneine, carotenoids and melanins — display strong antioxidant activity *in vitro*, which has turned macromycetes, and particularly medicinal and wild edible mushrooms, into a valued and renewable source of natural antioxidants [4, p. 1899]. This dual, biological and applied significance places fungal antioxidant systems at the intersection of cell biology, biotechnology and biodiversity conservation. The present review summarizes the main enzymatic and non-enzymatic antioxidant systems of fungi, the regulation of their oxidative stress response, and the diversity and applied potential of fungal antioxidant metabolites.

AIM OF THE STUDY

The aim of the present work was to review and synthesize current knowledge on the antioxidant systems and the oxidative stress response of fungi, focusing on three directions: (1) the enzymatic and non-enzymatic (metabolite) antioxidant defenses; (2) the transcriptional regulation of the oxidative stress response; and (3) the diversity and applied potential of fungal antioxidant metabolites — in order to highlight fungal biodiversity as a valuable, renewable reservoir of natural antioxidant compounds.

MATERIALS AND METHODS

This paper was conceived as a narrative review based on the analysis of the specialized scientific literature. Relevant publications were retrieved from international bibliographic databases and publisher platforms — PubMed, Scopus, ScienceDirect, Google Scholar, SpringerLink, MDPI and Frontiers — as well as from the National Bibliometric Instrument of the Republic of Moldova (IBN). The search combined keywords such as “fungal oxidative stress”, “antioxidant systems in fungi”, “reactive oxygen species”, “ergothioneine”, “fungal melanin”, “mushroom polysaccharides antioxidant”, “Yap1” and “fungal secondary metabolites with antioxidant activity”, used individually and in combination. Preference was given to peer-reviewed reviews and original articles published mainly over the last two decades (up to 2026), covering both model and filamentous fungi and macromycetes (medicinal and wild edible mushrooms). The selected sources were assessed for relevance, and the extracted information was organized and analyzed thematically, focusing on the enzymatic and non-enzymatic antioxidant systems, the regulation of the oxidative stress response, and fungal metabolites with antioxidant activity.

RESULTS AND DISCUSSION

1. Oxidative stress and sources of ROS in fungi

In fungal cells, ROS arise from both endogenous and exogenous sources. The main internal source is the mitochondrial electron transport chain, complemented by nicotinamide adenine dinucleotide phosphate reduced (NADPH) oxidases (Nox), peroxisomal fatty-acid β-oxidation and various cellular oxidases [1, p. 333]. Externally, ROS generation is amplified by environmental factors — ultraviolet radiation, extreme temperatures, desiccation, heavy metals and xenobiotics — by competition with other microorganisms and, in pathogenic species, by the oxidative burst of the host's immune cells [2, p. 235–250]. A moderate, controlled level of ROS is physiologically necessary, acting as a signal in growth, hyphal differentiation, morphogenesis and sporulation [1, p. 333]. When the rate of ROS formation exceeds the cell's neutralizing capacity, oxidative stress sets in: membrane lipids undergo peroxidation, proteins are carbonylated and DNA is damaged, compromising cell viability [1, p. 333; 2, p. 235–250]. Counteracting this imbalance is precisely the role of the antioxidant systems presented below.

2. Enzymatic antioxidant systems

The enzymatic defense represents the first and most efficient line against ROS in fungi. Superoxide dismutases (SODs) initiate detoxification by dismutating the superoxide anion (O_2^-) into hydrogen peroxide (H_2O_2); fungal cells typically express several isoforms, including a cytosolic Cu/Zn-SOD and a mitochondrial Mn-SOD [1, p. 333]. The resulting hydrogen peroxide is then removed by catalases, which decompose it into water and oxygen, and by glutathione peroxidases and peroxiredoxins, which reduce both H_2O_2 and organic peroxides [2, p. 235–250]. The activity of these peroxidases depends on two central thiol-based redox systems — the glutathione/glutaredoxin and the thioredoxin/thioredoxin reductase systems — which provide reducing power, regenerate the oxidized enzymes and maintain the intracellular redox balance, ultimately at the expense of NADPH [1, p. 333; 2, p. 235–250]. In pathogenic species such as *Candida albicans*, the coordinated action of catalase, glutathione and thioredoxin pathways is essential for surviving host-imposed oxidative stress [5, p. e0137750].

3. Non-enzymatic and metabolite antioxidants

Alongside enzymes, fungi accumulate a range of low-molecular-weight and metabolite antioxidants. Glutathione is the major cellular thiol: it buffers the intracellular redox potential, directly scavenges ROS and serves as the cofactor of glutathione peroxidases and glutaredoxins [1, p. 333]. A particularly important fungal antioxidant is ergothioneine, a sulfur-containing histidine derivative synthesized by many fungi, which accumulates in the cell and protects proteins, lipids and DNA against oxidative damage [6, p. 35306]. Melanins — dark pigments deposited mainly in the cell wall — act as efficient scavengers of ROS and free radicals and shield the cell against ultraviolet radiation and environmental stress, contributing to survival and, in pathogens, to virulence [7, p. 491–495]. Further contributions come from carotenoids, which quench singlet oxygen, and from compatible solutes such as mannitol and trehalose, which also display radical-scavenging properties. Many of these metabolites are, moreover, valuable bioactive compounds, as discussed below.

4. Regulation of the oxidative stress response

The antioxidant defenses are not entirely constitutive but are induced in a coordinated manner, mainly through transcriptional regulation [2, p. 235–250]. In yeast, the central sensor is Yap1, an AP-1-like basic leucine zipper (bZIP) transcription factor. Under basal conditions Yap1 is continuously exported from the nucleus, but upon exposure to hydrogen peroxide specific cysteine residues are oxidized — a reaction relayed by the thiol peroxidase Gpx3/Orp1 — generating intramolecular disulfide bonds that mask its nuclear export signal [8, p. 917–921]. As a consequence, Yap1 accumulates in the nucleus and activates a broad regulon of antioxidant and detoxification genes, including those encoding catalase, superoxide dismutase, glutathione biosynthesis enzymes and the thioredoxin system [8, p. 917–921]. Functionally equivalent AP-1-like regulators operate in other fungi — Cap1 in *Candida albicans* and Pap1 in fission yeast — frequently acting together with the response regulator Skn7 and the Hog1 mitogen-activated protein kinase (MAPK) pathway [9, p. 245–258]. This network couples ROS sensing to the timely deployment of the defenses described above.

5. Fungal antioxidant metabolites of applied and biodiversity interest

Macrofungi are among the richest natural sources of antioxidant compounds, which explains their growing use in nutraceuticals, functional foods and pharmaceuticals. The antioxidant activity of mushroom extracts is attributed mainly to phenolic compounds — phenolic acids and flavonoids — and to polysaccharides, particularly β-glucans, whose radical-scavenging and reducing capacity is routinely demonstrated by DPPH (2,2-diphenyl-1-picrylhydrazyl), ABTS (2,2-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) and FRAP (ferric reducing antioxidant power) assays [4, p. 1899; 10, p. 674–678]. Medicinal species such as *Ganoderma lucidum* [11, p. 2725] and widely consumed wild edible mushrooms, including *Boletus edulis* [12, p. 313905], are recognized for their high antioxidant potential. Beyond this applied value, the findings carry an ecological dimension directly relevant to the present symposium: fungal diversity constitutes a vast and still largely unexplored reservoir of bioactive antioxidant molecules. The conservation of natural habitats such as the “Codrii” Reserve is therefore essential not only for preserving species, but also for safeguarding a genetic and biochemical resource of considerable scientific and biotechnological value.

CONCLUSIONS

Fungi rely on an integrated and finely regulated antioxidant system, combining enzymatic components — superoxide dismutases, catalases and the peroxidase, nonenzymatic glutathione and thioredoxin systems — with metabolite antioxidants such as glutathione, ergothioneine and melanins, coordinated at the transcriptional level by AP-1-like regulators. This network allows them to preserve redox homeostasis under both endogenous and environmentally imposed oxidative stress. At the same time, many of these fungal metabolites display marked antioxidant activity and represent valuable bioactive compounds for the food, nutraceutical and pharmaceutical fields. Fungal biodiversity therefore constitutes a significant reservoir of natural antioxidants, and the conservation of protected areas such as the "Codrii" Reserve is essential for safeguarding both species diversity and the associated biochemical resources.

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