Chapter 2
Fungi as a Gold Mine of Antioxidants

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Contents

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2.1 Introduction

There has been a current upsurge in the medical implications of free radicals and related species during the past several decades. These chemical species are integral components produced during normal biochemical and physiological processes but lead to oxidative stress when produced in excess and cause potential damage to cells. A wide range of nonenzymatic and enzymatic antioxidant defenses exists to counteract the damaging effects of free radicals. There exist epidemiological evidence correlating higher intake of antioxidant-rich foodstuffs with greater free radical neutralizing potential to lower incidence of several human morbidities or mortalities. Novel biomolecules and the use of functional foods enriched with antioxidants are milestones to newer approaches to reduce free radical damage. So, the putative antioxidants from different sources play a significant role in controlling oxidative stress and reduce the incidence of concerned diseases (Kalam et al. 2012).

One of the exciting moves in microbial sciences has been to refocus and revitalize efforts to mine the secondary fungal metabolome (SMs) and natural products (NPs). The magnitude of biosynthetic gene clusters (BGCs) combined with the historical number of sequenced genomes in a single filamentous fungal genome suggests that the secondary metabolite wealth of filamentous fungi is largely untapped. Mining algorithms and scalable expression platforms have greatly increased access to the chemical repertoire of secondary metabolites derived from fungi (Keller 2019).

Fungi have a long and intimate relationship with the human, especially on the chemical level. The realization that fungi were the source of both dangerous and beneficent compounds was brought to light in the 1960s by the aflatoxin poisoning case Turkey X disease, and the discovery of the first wide-spectrum antibiotic, penicillin, was considered World War II2's wonder drug (Devi et al. 2020; Yadav 2019; Yadav et al. 2018, 2019a). These bioactive molecules may be fungal secondary metabolites or primary metabolite (natural products NPs), these metabolites are produced by specific fungal taxa principally by filamentous fungi belonging to the Pezizomycotina, Ascomycete class, and many Basidiomycete classes (viz., Agaricomycetes and Exobasidiomycetes), additionally by unexpected taxa such as *Kluyveromyces lactis*, in which pulcherrimin gene recently located (Keller 2019; Yadav et al. 2019b).

Secondary metabolites are derived from core metabolic pathways and primary metabolite reservoirs, with acyl-CoAs being the essential initial building blocks that feed into polyketide synthesis (e.g., aflatoxin) and terpene (e.g., carotene) secondary metabolites and amino acids that are used to synthesize non-ribosomal secondary metabolites, for example, penicillin. In contrast to genes that are required for the synthesis of a primary metabolite that is dispersed throughout the fungal genome (Krause et al. 2018; Rastegari et al. 2019a, b). About 1500 compounds have been isolated from fungi between 1993 and 2001. More than half of them exhibited antifungal, antibacterial, or antitumor activity was discovered between 2009 and 2013 confirmed as prospective fungal secondary metabolites (Schueffler and Anke 2014).

Bioprospecting is described as the search for naturally occurring chemical compounds and biological material, especially in extreme harsh habitats under different stressors or biodiversity-rich environments (Abdel-Azeem et al. 2012; Yadav et al. 2020). There are many lines of proof supporting ecological fitness roles for fungal secondary metabolites, involving the assessment of regulatory cascades. These studies showed that many genes that encode secondary metabolites are regulated in a manner congruent with fungal development or in response to stressors (both abiotic and biotic) and that overproduction or loss will alter the specific fungus development and survival (Keller 2019).

Fungi are the most versatile and plentiful group on the planet and since they mimic the animal system, they are an excellent candidate for the development of bioactive metabolites (Kour et al. 2019). Molecular test methods recently suggested there were up to 5.1 million fungal species, of which only around 100,000 have been recorded in the literature. They involve 14,000 mushroom species, 5000 macro fungi, and more than 1800 fungi with medicinal and pharmacological therapeutic properties (Kirk et al. 2001; Abdel-Azeem et al. 2021). The different fungal kingdoms are classified into many phyla, including Ascomycota (sac fungi) and Basidiomycota (club fungi), Zygomycota and Blastocladiomycota and Chytridiomycota. Most pharmacological and therapeutic studies focus solely on Ascomycota and Basidiomycota strains or species (Cui et al. 2015), while Zygomycota is relatively less investigated. However, the majority of those in the diverse, high-antioxidant capacity, the secondary metabolite-rich endophytic community of fungi also belong to the divisions Ascomycota and Basidiomycota, with few members known as *Mucor* and *Umbelopsis* of the genera Zygomycota (Cui et al. 2015). The adaptation and morphogenesis of host plants by protecting against insects, predators, microbial pathogens, and latent pathogens are being played an important role by endophytic fungi. Similarly, Mucorales of Zygomycota is known as the Entomophthoral (pathogens of insects) sister group, Mucorales' pathogenic nature is believed to be caused mainly by endocellular excretions and the development of subtilizers, chitinases, proteinases, and antioxidant proteins (e.g., superoxide dismutase, catalase, and peroxidase) (Freimoser et al. 2003).

2.2 Oxidative Stress: Basic Overview

Oxidation is essential for many living organisms to produce energy to fuel biological processes (Yang et al. 2002). Oxygen is a highly reactive atom that is able to become part of massively damaging molecules commonly called "free radicals". Free radicals are capable of attacking the healthy cells of the body. Cellular destruction is caused by free radicals, in the form of reactive nitrogen species (RNS) or mainly in the form of reactive oxygen species (ROS) during normal metabolic processes in aerobic cells. Free radicals derived from molecular oxygen are the most important class of radical species formulated in living systems (Miller et al. 1990). A free radical is categorized as any atom or molecule with unpaired electrons in the outer orbit, which are usually unstable and very reactive (Gutteridge and Halliwell 2000). Oxidative stress is known as an imbalance in free radical production, as a result of overproduction of ROS or loss of natural antioxidant defenses. Overproduction can contribute to lipid, DNA, or protein oxidation, and is a major contributor to aging (Barja 2004), degenerative diseases such as cancer (Valko et al. 2006b), cardiovascular disease (Shah and Channon 2004), compromised immune function, inflammation, and renal failure (Valko et al. 2006a). For the past 40 years, oxidative stress has been progressively recognized as a contributing factor in aging and different forms of pathophysiology generally associated with aging (Hybertson et al. 2011).

Oxidant signals interfere in aerobic cells with the otherwise usual natural metabolic activity of ROS, such as; cell proliferation, differentiation, and apoptosis. When such damage occurs, there is cell toxicity leading to health ramifications (Suzuki et al. 2010). Mitochondria are often the first victim of a free radical attack because the lipid membrane is very susceptible to ROS degradation; this attack is called lipid peroxidation. ROS interaction with lipid molecules produces new free radicals; superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydrogen radicals ($OH^\bullet$). Then, these radical groups interact cytotoxically with biological systems (Barros et al. 2007). The relationship between antioxidant defense and ROS production is usually a representation of the degree of oxidative stress (Suzuki et al. 2010). Different free radicals involved in oxidative stress have different biological, chemical, and physical properties, including hydroxyl, alkoxyl, peroxyl, superoxide, nitric oxide, sulfur, and nitrogen-centered radicals (Niki 2010). The free radical scavenging capacity is influenced by several factors; the rate and number of radical molecules scavenged and the fate of antioxidant-derived radicals. The fate of this radical is also an important consideration of antioxidant efficacy (Niki and Noguchi 2000). There are many factors that impact the free radical scavenging capacity like, interaction with other antioxidants, concentration, mobility in the environment, and the adsorption, distribution, retention, and metabolism of the antioxidant compounds, the rate and number of radical molecules scavenged (Niki and Noguchi 2000; Niki 2010). When an active radical is scavenged by an antioxidant compound, a stable non-radical product is formed. At the same time the antioxidant yields one antioxidant-derived radical. The fate of this radical is also a significant consideration of antioxidant effectiveness (Niki and Noguchi 2000) (Fig. 2.1).

2.2.1 Oxidative Stress as "Mother" of Many Human Diseases at Strong Clinical Impact

Oxidative stress can be considered "mother" of numerous human diseases, which are life-threatening. Oxidative stress is a condition in which oxidation surpasses the antioxidant reactions, causing an imbalance between oxidative and antioxidant

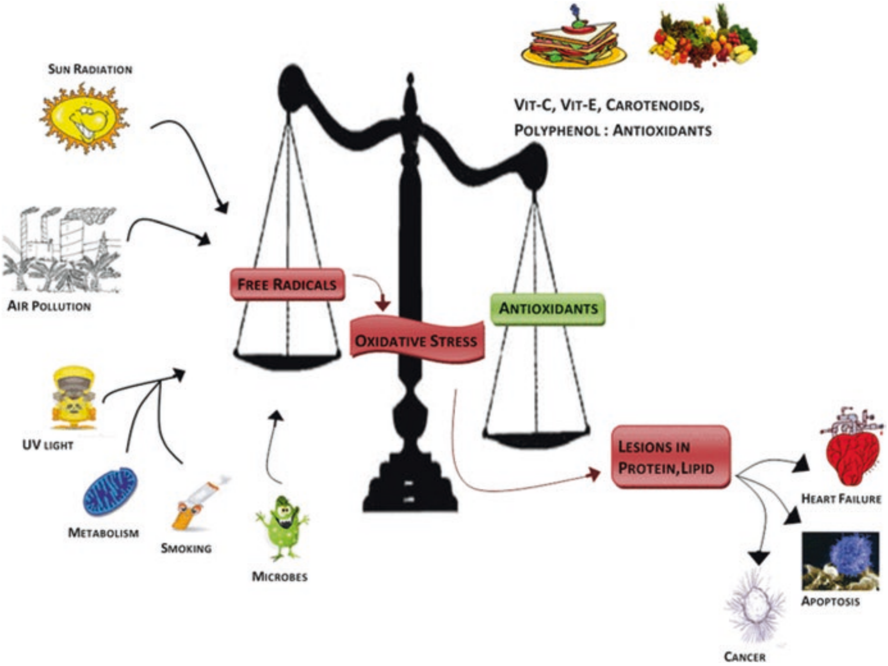

Fig. 2.1 Oxidative modifications of biomolecules. In normal physiological conditions, and how it ultimately causes various diseases. (Adapted from http://robinthomas.biz/so-what-causes-oxidative-stress-anyway/)

systems, with the predominance of reactive oxygen species ROS. Under typical conditions, ROS are kept up at physiological levels by many endogenous antioxidant systems, as superoxide dismutase, glutathione peroxidases, catalase, lactopeptidases, glutathione reductase, and others. However, if active ROS are massively created, the balance between the formation and the removal of these species is lost. Resulting oxidative damage can be generated from both endogenous and exogenous sources. Endogenous ROS are produced in normal metabolic reactions. Exogenous ROS derive by exposure to environmental pollutants, cigarette smoke, and consumption of alcohol in excess, exposure to ionizing radiations, viral and bacterial infections, and others as mention before. Individual, hereditary factors, and lifestyle are the major determinants of oxidative stress. So, we are going to refer to some pathology favored by detrimental impacts of ROS, responsible for morbidity and death (Cacciapuoti 2016).

Aging is a process characterized by the progressive depletion of organ and tissue function. The oxidative stress theory of aging is based on the hypothesis that age-associated functional losses are due to the accumulation of ROS-induced damages. Simultaneously, oxidative stress is included in many age-related conditions (viz., cardiovascular diseases (CVDs), chronic kidney disease, neurodegenerative diseases, chronic obstructive pulmonary disease, and cancer), including frailty and sarcopenia. Various types of oxidative stress biomarkers have been recognized and may provide significant information about the effectiveness of the treatment, guiding the selection of the most effective drug for patients and, if especially relevant from a pathophysiological point of view, acting on a particular therapeutic target. Given the significant role of oxidative stress is the pathogenesis of clinical conditions and aging (Liguori et al. 2018). The cancer-induction is a multifactorial process that involves many factors, as physical, chemical, genetic, and environmental factors. Recent knowledge's in ROS biology elucidate that free radicals control different features of tumor development involving inflammation, transformation, survival, proliferation of cancers' cells, invasion, angiogenesis, and metastasis (Waris and Ahsan 2006). Particularly, free radicals directly or indirectly act, via DNA damage, on gene expression and signaling at the cellular levels. In progression, the major impacts of ROS on tumor genesis and some clinical complications (Cacciapuoti 2016).

Youn et al. (2014) hypothesized that ROS produced in vascular smooth muscle cells (VSMC) play a significant role in the development of obesity, causing a condition of overweight due to glucose intolerance, leptin resistance, and inflammation. On the other hand, the expansion of visceral adipose tissue caused by overconsumption of food, increases visceral adipose tissue. As visceral fat stores expand, adipocytes generate increased ROS levels and metabolic syndrome. Therefore, two conditions (oxidative stress and obesity) can be considered correspondingly as cause and impact one of another. Indication loss in nerve structure and function leads to progressive brain damage and neurodegeneration as a complication of neurogenerative diseases. Apart from environmental or genetic factors, oxidative stress mainly contributes to neuro degeneration. Especially, ROS have been implicated in the progression of Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Cacciapuoti (2016), in the case of Parkinson's disease, felt that majority of cases of PD is idiopathic. Exposure to some substances (e.g., pesticides, toxins, organic solvent) is viral and bacterial (Gomez-Cabrera et al. 2005). Oxidative stress also intervenes in other pathologic conditions commonly occurring among human diseases, such as chronic obstructive pulmonary disease, chronic fatigue syndrome, and skin disease (Cacciapuoti 2016).

2.3 Meet Your Free Radical Surveyors: Antioxidants

Antioxidants are a wide group of compounds that constitute the primary line of defense against free radical stress. They are fundamental for keeping up ideal wellbeing as defensive operators that can deactivate or stabilize free radicals (Kalam et al. 2012). Free radical damage complication and ramification raises the require for admissions of antioxidants, free radical hoist due to contamination, cigarette smoke, ailment, and therapeutics operators. Recognizable proof of pharmacologically potential antioxidants expanded staggeringly as they show no side impact for us in preventive medication and food industry.

Antioxidants are a family of compounds considered to be the leading endeavor against a number of age-related issues such as Alzheimer and many diseases. Termed as a wonder element; antioxidants are basic to great health and well-being as the concept of well-being enhancement has ended up a genuine portion of healthcare. The capacity to utilize oxygen has given people the advantage of metabolizing fats, proteins, and carbohydrates for vitality (Percival 1998). Humans have advanced an exceedingly complicated antioxidant defense technique to combat the harmful impacts of free radicals. These incorporate both endogenous and exogenous components, which work with intelligence and synergistically to neutralize free radicals (Liebler 1993). These components are (1) Antioxidant chemicals (Superoxide Dismutase, Glutathione peroxidase, and Catalase), (2) Metal official proteins (Ferritin, Lactoferrin, Egg whites, and Ceruloplasmin), (3) Nutrient-derived antioxidants (Ascorbic corrosive, Tocopherols, Tocotrienols, Carotenoids, Glutathione, and Lipoic corrosive), and (4) Phytonutrients (Flavonoids, Phenolic corrosive, Stilbenes, Tannins, and Carotenoids). The sum of antioxidants is calculated as ORAC values, that is, Oxygen Radical Absorbance Capacity, which could be a degree of the capacity of nourishments to stifle hurtful oxygen free radicals that can harm the human body.

The ORAC values for two glasses of dark tea are proportionate to that of one glass of ruddy wine or seven glasses of orange juice or consuming 20 glasses of apple juice. In addition to, dark chocolate snack within a balanced diet can enhance DNA resistance to oxidative stress in healthy subjects (Spadafranca et al. 2010). Antioxidants are intimately elaborated in the prevention of cellular damage the general pathway for cancer, aging, and different disease. DNA damage and other cellular organelles by free radicals occupy the highest position in the onset and development of diseases. For instance, Atherosclerosis and its complexity most particularly Coronary Heart Disease (CHD) continue to be the main cause of premature death in the developing world. Polyunsaturated fatty acid residues in lipoproteins have a chemical configuration that makes them a particularly vulnerable target for free radical oxidation. Studies have illustrated an inverse relationship between vitamin C intake and cardiovascular disease mortality in humans. In hypercholesterolemic persons, treatment with a combination of vitamin E and slow-release vitamin C slows down atherosclerotic progression.

On the other hand, antioxidants in plant cells mainly include glutathione, tocopherol, ascorbate, betaine, proline, and others, which are also information-rich redox buffers and important redox signaling components that interact with cellular organelles. As an unfortunate ramification of aerobic life for higher plants, ROS are formed by partial reduction of molecular oxygen. The enzymatic and nonenzymatic antioxidants in higher plant cells can protect their cells from oxidative damage by scavenging ROS. Thus, a special investigation is given to ROS and ROS-antioxidant interaction as a metabolic interface for various types of signals derived from metabolisms and the changing environment. Besides exacerbating cellular damage, ROS act as ubiquitous signal molecules in higher plants as well as a central ingredient in stress responses (Kalam et al. 2012). Other than the health advancing impacts from the utilization of natural antioxidants, avoidance of oxidation is vital in other areas too. Within the nourishment industry, oxidation influences the dietary esteem of food and can cause rancidity of color, flavor, and texture. Microbial decay may be a huge issue for nourishment producers. Customarily salt, sulfite, and antimicrobial compounds have been used to restrain the development of microorganisms in food items; in any case, usually not perfect. Moreover, utilization of synesthetic antioxidants such as butylated hydroxyanisole (BHA) and butylated hydroxyltoluene (BHT) are presently known to have a negative effect on health (Branen 1975; Larson 1988).

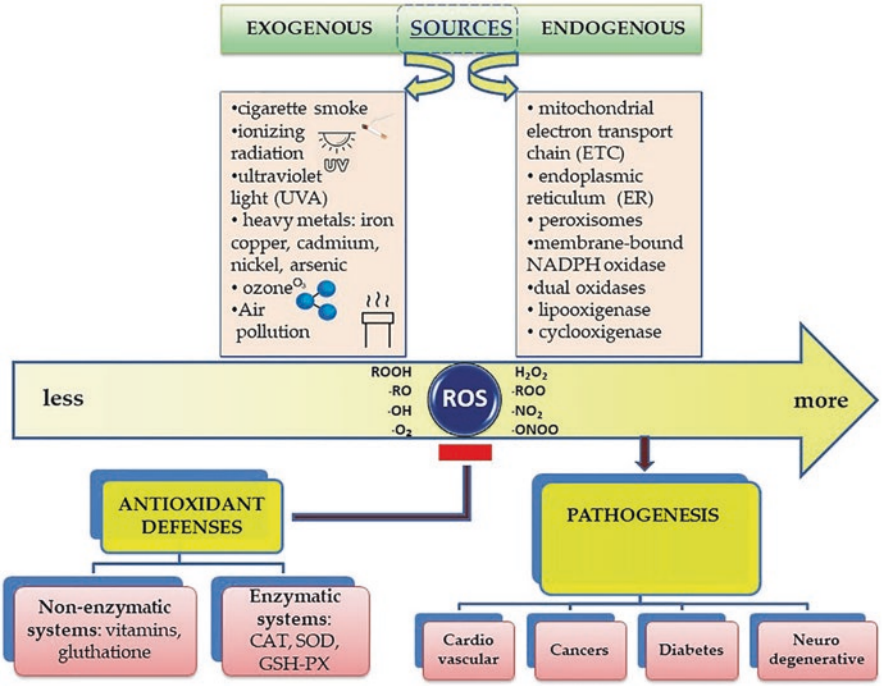

Fig. 2.2 The sources of free radicals and their effects on human body (Kalam et al. 2012)

With expanding consumer awareness of food preparation, controversy has surrounded the use of synthetic antioxidants like, BHT and BHA as food additives, which lead to a particular interest in safe preservatives from natural sources. A wide extent of additives can be utilized alone or as a mix. A mix can create a less costly item without compromising proficiency. For example, tocopherols may be mixed with another prevalent antioxidant, such as rosemary extract. The food preservation market is expected to reach €2 billion by 2018, in spite of the fact that natural preservatives are projected to contribute to the smallest share of the markets. The European market alone is extended from €79 million, recorded in 2011 to €188 million by 2018. With consumer perception with respect to the benefits of natural additives and health hazards related with consumption of foods preserved with the utilization of nourishments protected chemically, natural preservatives, such as antioxidants are in demand (Smith 2014). New trends launched lately depend on using fungi as a potential source of antioxidants that can be utilized to prevent oxidative damage and, as such, can decrease their harmful impacts on humans and animals alike (Smith 2014) (Fig. 2.2).

2.4 Antioxidant Classification

Antioxidants can be classified into two major types based on their source, that is, natural and synthetic antioxidants (schematic representation of the classification of antioxidants is shown in Fig. 2.3).

2.4.1 Natural Antioxidants

Either is synthesized in the human body through a metabolic process or is supplemented from other characteristic sources and their action depends very much upon their physical and chemical properties and component of action. This could be advance separated into two categories, that is, enzymatic antioxidants and nonenzymatic antioxidants (Mamta et al. 2013).

2.4.2 Enzymatic Antioxidants

Enzymatic antioxidants are uniquely produced in the human body and can be subdivided into primary and secondary antioxidants (Mamta et al. 2013) (Fig. 2.4).

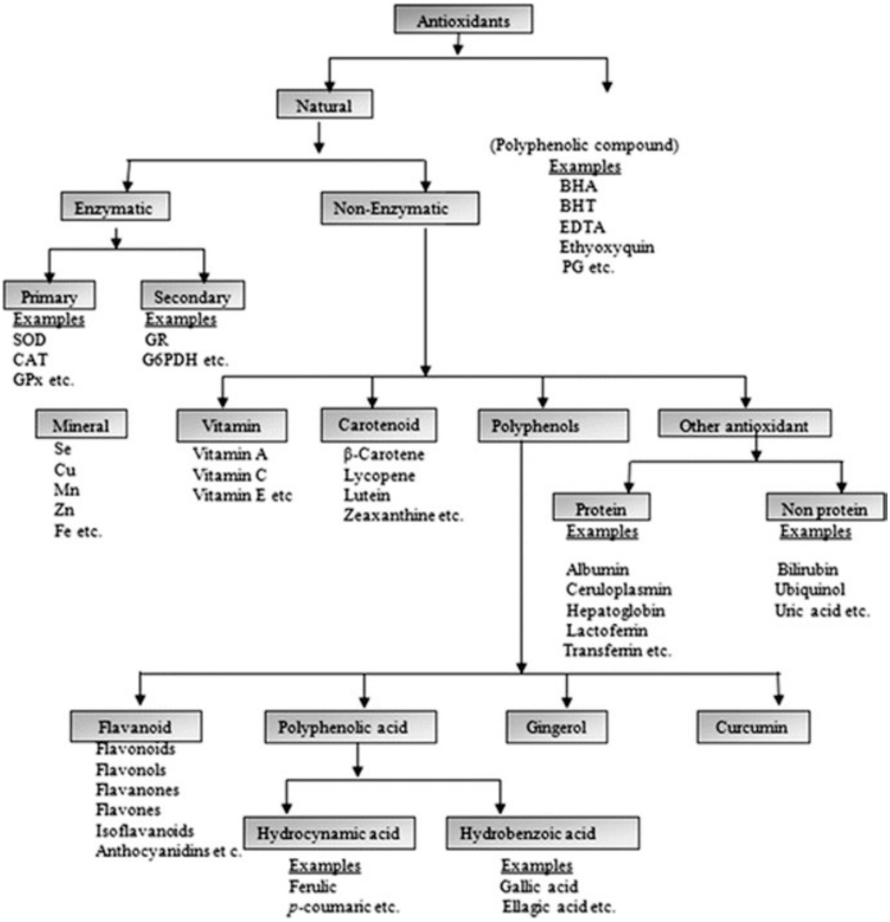

Fig. 2.3 Schematic representation of antioxidants classification (Mamta et al. 2013)

2.4.2.1 Primary Antioxidants

Primary antioxidants basically include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) as portrayed below. Superoxide dismutase (SOD) enzyme is found in both the dermis and the epidermis. It expels the superoxide radical (O_2^-) and repairs the body cells harmed by free radicals. SOD catalyzes the reduction of superoxide anions to hydrogen peroxide. SOD is additionally known to compete with nitric oxide (NO) for superoxide anion, which inactivates NO to create peroxynitrite. Subsequently, scavenging superoxide anions promotes the activity of NO (Chakraborty et al. 2009).

$$2O_2^{??} + 2H \overset{SOD}{?} H_2O + O_2$$

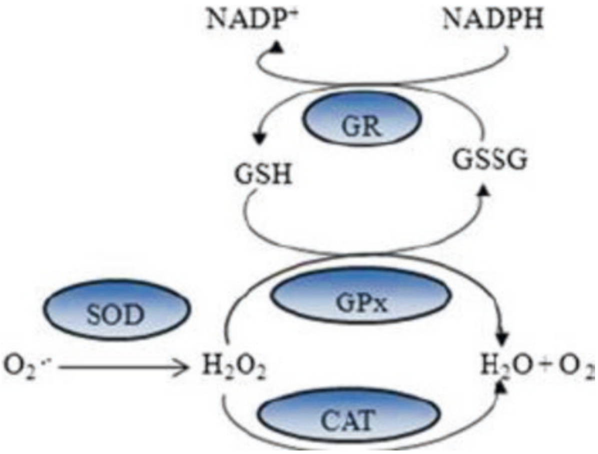

Fig. 2.4 Outline of the mechanism of enzymatic antioxidants in the removal of free radicals (Mamta et al 2013)

Catalase enzyme (CAT) is found within the blood and most of the living cells and breaks down H_2O_2 into water and oxygen. Catalase besides glucose peroxidase is additionally utilized commercially for the conservation of the natural product juices, a cream consisting of egg yolk and serving of mixed greens by evacuating the oxygen (Chakraborty et al. 2009).

$$2H_2O_2 \overset{\mathrm{CAT}}{?} 2H_2O + O_2$$

Glutathione peroxidase (GPx) could be a gather of selenium-dependent enzymes, and it comprises cytosolic, plasma, phospholipid hydroperoxide, and gastrointestinal glutathione peroxidase. GPx (cellular and plasma) catalyzes the response of H_2O_2 by decreased glutathione (GSH); as a result, oxidized glutathione (GSSG) is delivered and it is once more restored to its reduced form by glutathione reductase (GR) and reduced nicotinamide adenine dinucleotide phosphate (NADPH) (Chakraborty et al. 2009).

$$2GSH + H_2O_2 \overset{GPx}{?} \mathrm{GSSG} + 2H_2O$$

2.4.2.2 Secondary Antioxidant

Secondary antioxidant incorporates glutathione reductase (GR) and glucose-6-phosphate dehydrogenase (G6PDH). G6PDH creates NADPH. GR is required to reuse the reduced glutathione (GSH) utilizing secondary enzyme GR and NADPH.

$$\mathrm{GSSG} + \mathrm{NADP} \overset{GR}{?} \mathrm{NADP} + 2GSH$$

Glutathione is a cysteine-containing peptide-type antioxidant and is synthesized in the body cells. The thiol group in its cysteine moiety is a reducing agent and can be reversibly oxidized and reduced. An elevated level of glutathione was found within the cells (~3100 μg/g of tissue), kept up within the reduced form (GSH) by the protein GR and in turn decreases other metabolites and enzyme systems, such as ascorbate. Due to its elevated concentration and its part in maintaining the redox state within the cells, it is considered one of the foremost critical cellular antioxidants (Hissin and Hilf 1976).

2.4.3 Nonenzymatic Antioxidants

These are a class of antioxidants that are not normally present in the body, but must be included in the diet for proper metabolism. Vitamins, carotenoids, minerals, polyphenols, and other antioxidants are some of the identified nonenzymatic antioxidants as mentioned below (Veysi et al. 2007).

2.4.3.1 Minerals

Minerals are needed for the proper functioning of the enzymes in the body cells. It is understood that their absence affects the metabolism of several macromolecules. Minerals include selenium, copper, iron, zinc, manganese, and so on. They serve as cofactors for the antioxidant enzymes. Iron (Fe) is the most common trace metal used in the biological system to bind to the protein. The free iron concentration is naturally very small, and small iron-binding protein concentrations promote ROS formation, lipid peroxidation, and oxidative stress (Dabbagh et al. 1994). The intake of iron thus helps to reduce oxidative stress. Magnesium (Mg) is a glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD) cofactor associated with pentose cycle that catalyzes NADPH production during glucose metabolism and thus maintains a proper GSH to GSSG ratio and a normal redox state in cells. Magnesium deficiency decreases GR activity and GSSG aren't reduced to GSH, thereby resulting in oxidative cell damage (Fang et al. 2002). Selenium (Se) is also an essential enzymatic antioxidant element. In the existence of selenium (Se), glutathione peroxidase (GPx) provides excellent protection against lipid oxidation and serves to protect the cell membrane and participates in the metabolism of H_2O_2 and hydroxyperoxide of lipids. (Se) thus acts like vitamin E and can be supplemented with vitamin E and is used to reduce cancer risk and cardiovascular disease (Sikora et al. 2008). Copper (Cu), Zinc (Zn), and Manganese (Mn) SOD is an enzyme class consisting of different forms of SODs, based on their metal cofactor including Cu–Zn and Mn. Cu–Zn SOD is located in the cytosol with

Cu and Zn at their active sites that aid in the conduction of protons, while Mn-SOD is located in the mitochondria and has Mn at their active site. Those metals are the source of antioxidant activities of SOD (Mamta et al. 2013).

2.4.3.2 Vitamins

Vitamins are the micronutrient class necessary to act properly in the body's antioxidant enzyme system, such as vitamin A, vitamin C, vitamin E, and vitamin B. They are not synthesizable in our body and therefore have to be replaced in the dietary intake (Rastegari et al. 2020). Vitamin A helps to improve night vision and epithelial cells in the mucous membranes and skin. This also strengthens the immune system because of its antioxidant properties and is present in three primary forms: retinol, 3,4-didehydroretinol, and 3-hydroxyretinol. Sweet potatoes, carrots, milk, egg yolks, and mozzarella cheese are the principal sources of vitamin A. Vitamin C is soluble in water and is also known as ascorbic acid. It is found in fruits (mostly citrus), vegetables, cereals, beef, poultry, and fish, and so on. It helps to avoid some of the DNA damage caused by free radicals, which can lead to the aging process and disease progressions, such as cancer, heart disease, and arthritis. Vitamin E is a vitamin that is soluble in lipids. It consists of eight various forms such as α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol. It is most common in almonds, safflower oil, soybean oils, wheat germ oil, nuts, broccoli, fish oil, and so on, α-tocopherol exhibits the highest bioavailability and is the most significant lipid-soluble antioxidant that reacts with the lipid radical and preserves the membranes from lipid peroxidation; as a result, oxidized α-tocopheroxyl radicals are generated, which can be restored to the reduced form through reduction by many other antioxidants, such as ascorbate and retinol (Mamta et al. 2013).

2.4.3.3 Carotenoid

Carotenoid is formed of β-carotene, lycopene, lutein, and zeaxanthin. They are colored compounds found in fruits and vegetables that are fat-soluble. β-Carotene is mostly found in radish-orange-green foods, including carrots, sweet potatoes, apricots, pumpkin, mangoes and cantaloupe, together with some green and leafy vegetables, such as spinach and kale. In green leafy vegetables such as collard greens, spinach, and kale, lutein is prevalent (Hamid et al. 2010). Lutein is best known to play a role in protecting the retina from dangerous free radical activity and also helps to prevent atherosclerosis (Sikora et al. 2008). While there is no provitamin A production in lycopene, lutein, canthaxanthin, and zeaxanthin, β-carotene is known as a precursor to vitamin A (Fang et al. 2002). Tomatoes are a good source of lycopene and zeaxanthin is a good source of spinach. Lycopene is a powerful antioxidant and is the most effective compound contained in strawberries, watermelon, guava, papaya, apricots, pink grapefruit, and other foods to eliminate singlet oxygen (Mamta et al. 2013).

2.4.3.4 Polyphenols

Polyphenols are a class of phytochemicals with notable antioxidant activity. Their antioxidant activities rely on our physical and chemical characteristics, which depending on their molecular structures, manage the metabolism (Ajila et al. 2011). These include phenolic acids, flavonoids, gingerol, curcumin, and so on (Kunwar and Priyadarsini 2011). Flavonoid is a significant component of polyphenolic compound and is found mainly in vegetables, fruits, grains, seeds, leaves, flowers, bark, and many more. Many of the spices, such as ginger and turmeric, are also excellent sources of polyphenolic compounds, for example, gingerol is derived from ginger rhizomes, whereas curcumin (diferuloylmethane) is the primary bioactive component of turmeric and is considered to have strong antioxidant activity. Curcumin is an outstanding scavenger of ROS, such as $O_2^{\bullet -}$ radicals, lipid peroxyl radicals ($LO_2^{\cdot}$), OH radicals and nitrogen dioxide ($NO_2^{\cdot}$) radicals that triggered oxidative stress. Curcumin has also been proven to prevent lipid peroxidation and GSH levels have also been shown to rise in epithelial cells leading to lower ROS development (Biswas et al. 2005).

2.4.3.5 Other Antioxidants

Albumin, ceruloplasmin, haptoglobin, and transferrin are the metal-binding transition proteins present in human plasma, binding with transition metals and controlling the development of metal-catalyzed free radicals. Albumin and ceruloplasmin are sequesters of copper ions, haptoglobin is a sequester of hemoglobin, and transferrin serves as the free iron sequester. Nonprotein antioxidants such as bilirubin, uric acids, and ubiquinol are antioxidants that prevent oxidation by scavenging free radicals (Papas 1998). Bilirubin is a catabolism final product of heme. It is a cytotoxic outcome that is lipid-soluble and must be eliminated. Nevertheless, bilirubin effectively scavenges peroxyl radical at in vitro model, micromolar concentrations (Stocker et al. 1987) and is considered the strongest antioxidant against lipid peroxidation. Uric acid is an effective antioxidant and a scavenger of singlet oxygen and radical substances. Urate reduces the oxidant developed by peroxide reaction with hemoglobin and prevents erythrocytes from peroxidative effects. Human plasma urate levels are about 300 μM, making it one of the most important antioxidants in humans (Ames et al. 1981). Coenzyme Q is also known as ubiquinol (Co Q) and is an antioxidant that is soluble in oil. This is generated by monovalent pathways in the body, in the heart, liver, kidney, pancreas, and so on. The action mechanism can occur in two ways. The reduced form of ubiquinol (CoQH) functions as a chain-breaking antioxidant in the first mechanism, reducing peroxyl (ROO) and alcoxyl radicals (LO) (Papas 1998).

$$\mathrm{CoQH} + ?\,ROO\,\mathrm{Q} + \mathrm{ROOH}$$

It interacts with vitamin E radical ($TO^{\bullet}$) and regenerates vitamin E in the second mechanism.

$$\mathrm{CoQH} + ?\,\mathrm{TO}\,\mathrm{Q}\,\mathrm{R} + OOH$$

2.4.4 *Synthetic Antioxidants*

Synthetic antioxidants are generated or synthesized artificially, using different techniques. They are mainly polyphenolic compounds that detect the free radicals and stop the chain reactions. Polyphenolic derivatives often involve more than one group of hydroxyls or methoxyes. Ethoxy quinine is the only heterocyclic, N-containing compound recorded to be used in food, especially animal feed, as an antioxidant. Most of the recorded synthetic phenolic antioxidants are *p*-substituted, whereas the *o*-substituted are mainly natural phenolic compounds. Because of their lower toxicity, the *p*-substituted substances are better suited. To boost their solubility in fats and oils and to reduce their toxicity, synthetic phenolic antioxidants are often substituted with alkyl groupings. Such organic compounds with antioxidant activity are widely used as preservatives for cosmetics in pharmaceuticals and for stabilizing food fat, oil, and lipid (Gupta and Sharma 2006). Such recent results about synthetic antioxidants have led the researchers to create new synthetic antioxidants in terms of their water solubility, stability, and nontoxicity. Features of some of the identified synthetic antioxidants, including butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ethylenediaminetetraactic acid (EDTA), 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (ethoxyquin), propyl gallate (PG), and tertiary butyl hydroquinone (TBHQ) (Hamid et al. 2010).

2.4.4.1 BHA

This is a monophenolic, lipid-soluble antioxidant and is best used in animal fat for lipid oxidation compared with vegetable oil (Wanasundara and Shahidi 2005).

2.4.4.2 BHT

This is also a monophenolic fat-soluble antioxidant but at high temperatures, it is much more stable than BHA and both function in synergy. Many antioxidant formulations that are currently available incorporate both of those antioxidants. BHA reacts with peroxy radicals to create a radical BHA phenoxy, which can, in turn, detach a hydrogen atom from the BHT hydroxyl group. The hydrogen radical provided by BHT regenerates BHA. The so-formed BHT radicals can interact with a radical peroxide and function as a chain terminator (Wanasundara and Shahidi 2005).

2.4.4.3 EDTA

EDTA is a widely used sequestrant, a water-soluble antioxidant that is applied to food, body care, and home products. It attaches with the trace minerals that may be present in the foodstuff, such as copper, iron, and nickel. If not inhibited, these minerals may result in discoloration, rancidity, and breakdown of the textures. Added as an antioxidant, EDTA helps to prevent oxygen from triggering changes in color and rancidity.

2.4.4.4 Ethoxyquin

It is chiefly used as an antioxidant to prevent carotenoid oxidation all through storage in animal feeds, vegetables, and fruits.

2.4.4.5 PG

This is an ester, created by gallic acid and propanol condensation. It works as an antioxidant that is used as a food additive to preserve primarily oils and fat in the foodstuff.

2.4.4.6 TBHQ

TBHQ is a remarkably efficient antioxidant to the diphenolic system. This is used as a preservative in food for unsaturated vegetable oils and other edible animal fats. Although in the presence of iron, it does not trigger discoloration and does not even alter the flavor or odor of the material to which it is introduced. It is used industrially as a stabilizer to restrict organic peroxide auto-polymerization. It can be used in biodiesel as a corrosion inhibitor. It is used as a fixative in perfumery, to lower the rate of evaporation and increase stability. It is also applied to additives to the varnishes, lacquers, resins, and field oil. It can be used individually or in conjunction with BHA or BHT (Said et al. 2002).

2.4.5 Natural Antioxidant versus Synthetic Antioxidant

Based on complex toxicity studies, synthetic antioxidants have been tested to ensure safety and approval for use in limited concentrations in foods. While synthetic antioxidants have been widely used in most countries, their safety remains in question (Shahidi 2005). An antioxidant should have two requirements to be declared safe:

its LD50 should not be less than 1000 mg/kg body weight and the antioxidant must have no noticeable impact on the growth of the experimental animal in long-term experiments at a level 100 times higher than that indicated for human consumption (Lehman et al. 1951). An antioxidant for use in food often needs comprehensive toxicological studies of its possible mutagenic, teratogenic, and carcinogenic actions (Yanishlieva et al. 2000). It has been shown that high concentrations of antioxidants can share a range of toxic properties (Shahidi 2005). BHT had negative effects on rat's liver, kidney, and lung due to their possible action as carcinogenesis, as per the Lanigan and Yamarik studies (2002). A few studies have shown that BHA and BHT are cytotoxic due to the carcinogenicity of BHA in the rodents' forestomach (Saito et al. 2003; Verhagen et al. 1991), therefore, governments have taken some steps to minimize the use of synthetic antioxidants in foods. It is clear that negative consequences of synthetic antioxidants only occur at elevated concentrations.

Meanwhile, several studies have shown that the amount of synthetic antioxidants commonly used in foods does not only have any harmful effects on humans, but also anticarcinogenic and antimutagenic qualities and other beneficial effects (Whysner et al. 1994; Hirose et al. 1999; Valenzuela et al. 2003; Williams et al. 1999). BHA and BHT show no cancer threat according to Williams et al. (1999) and may be anticarcinogenic at current rates of use. The safety of synthetic antioxidants during long-term consumption is still a controversial issue due to their potentially harmful effects. It seems rational that if there is a slight chance of synthetic antioxidants being toxic, we would seek to substitute them with natural antioxidants, which are more relevant to human nature. Using TG/DTA methodology, Santos et al. (2012) tested the thermal stability of industrial synthetic antioxidants and some natural antioxidants using both dynamic and isothermal (110 °C) research methods. They found that synthetic antioxidants showed thermal resistance in the following order: PG > TBHQ > BHA > BHT and natural antioxidants showed the following stability: α-tocopherol > caffeic acid > ferulic acid > gallic acid. Cruz et al. (2007) studied the thermal stability of three biomass-derived fractions with antioxidant activity (ethyl acetate soluble-fraction of *Eucalyptus globulus* acid hydrolysates, ethyl acetate soluble-fraction of red grape pomace auto-hydrolysis liquors after fermentation and distillation and water washing of the same feedstock) and two synthetic antioxidants in food is BHA and BHT. For assays lasting up to 120 min, the nonvolatile component, antioxidant activity, and the percentage of phenolic recovered during solid phase were assessed at 100, 150, or 200 °C. The tests showed higher thermal stability than BHA or BHT in the ethyl acetate soluble from acid hydrolysates of *Eucalyptus globulus* wood, from auto-hydrolysis and the washing of distilled red grape pomace. Furthermore, after the heating treatment, the naturally derived antioxidants displayed more antioxidant activity. Encapsulation has been proven to improve the thermal stability of natural antioxidants (Taghvaei et al. 2013). The Arabic gum encapsulated OLE improved soybean oil's thermal stability more than OLEs. The reason for this could be traced back to the protection of natural antioxidants by encapsulation against destructive factors. It can be established that certain natural antioxidants not only have a greater capacity for prevention of oxidation than synthetic antioxidants but also have greater thermal stability and can stay further active after heat treatment compared to synthetic antioxidants.

Taking into consideration the adverse effects of high concentrations of synthetic antioxidants and their poor thermal stability in the heat processing and frying of food products, the substitution of synthetic antioxidants with natural ones seems reasonable. There are plenty of natural antioxidants that can be derived from low-cost sources with more antioxidant activity and thermal stability than synthetic ones in different edible oils, according to several studies done over the past two decades. For instance, green tea extract derived from tea waste may be used in the food industry as the correct natural antioxidants. Additionally, extracts rich in rosemary and β-carotene and tocopherols can be used more often in the future. Several of these studies show that natural antioxidants can be extracted and applied in the edible oil industry, instead of synthetic ones. Both tea extract and rosemary extract have been proposed as an effective alternative for synthetic antioxidants in the research of Yanishlieva et al. (2000). The authors suggested that the health issues need to be resolved in future research for the use of natural antioxidants. Abo Nahas (2019) reported that the food industry is sighted on replacing synthetic antioxidants with natural antioxidants. He studied the utilization of fennel and chamomile extracts, rich in phenolic compounds, as natural antioxidants in biscuits and compared their performance with a synthetic 62 antioxidant vastly used, the butylated hydroxyl anisole (BHA).

The complete nutritional profile, free sugars, fatty acids, and antioxidant activity were estimated after baking immediately, also after 15, 30, 45, and 60 days of storage. The results showed that the incorporation of natural and synthetic additives did not cause significant changes in color or the nutritional value of biscuits when compared with control samples. Both natural and synthetic additives conferred similar antioxidant activity to the biscuits. Therefore, natural additives are a more convenient solution for consumers who prefer foods "free" from synthetic additives. Moreover, natural additives were given by aqueous extraction, an eco-friendly and safe process. The main focus of studies in this field over the past decade has been to add more powerful natural antioxidants, which were mainly from plant resources and were usually considered healthy. When we use olive extract at very low doses, for example, there is no need to examine the harmful effects of such extract on humans. Yet certain unrecognized natural antioxidants have been added, and the potential toxic effects on the human body need to be investigated. It has been shown that animal PHIs do have an adequate antioxidant activity and may be more efficient from plant resources and synthetic antioxidants than certain natural antioxidants. Further studies are required to apply animal PHIs in edible oils and evaluate the long-term stability of the oil, since the antioxidant activity was examined through model systems in most studies in this area (Fig. 2.5).

Fig. 2.5 Natural antioxidant versus synthetic antioxidant (Abo Nahas 2019)

2.5 Fungal Jewels

Fungi are the most diverse and plentiful group on the planet and they are a brilliant candidate for bioactive metabolite production due to their resemblance to the animal system. Recently, molecular screening methods claimed there are as many as 5.1 million species of fungi, of which only approximately 100,000 have been reported in the literature (Kirk et al. 2008; Yadav 2020). Among these fungi, 14,000 species are mushrooms, 5000 are macro fungi, and more than 1800 fungi have been identified as possessing pharmacological, therapeutic, and medicinal features (Kirk et al. 2008).

Higher Basidiomycetes represent a taxonomically, ecologically, and physiologically extremely diverse group of eukaryotic organisms. Recently, extensive research on these fungi has markedly increased mainly due to their potential use in a variety of biotechnological applications, particularly for the production of food, enzymes, dietary supplements, and pharmaceutical compounds (Cohen et al. 2002; Wasser 2002). Many pharmaceutical substances with unique properties were extracted from mushrooms. The cholesterol-lowering, antidiabetic, and immune-modulating compounds are ready for industrial trials and further commercialization, while others are in various stages of development. Some of these substances are not strictly pharmaceutical products (medicines) but rather they represent a novel class of dietary supplements or nutraceuticals. The most important new pharmaceutical products from medicinal mushrooms include polysaccharides, antioxidants, and lectins (Guillot and Konska 1997; Wasser 2002; Ng 2004). In the last few years, there has been significant interest in the use of mushrooms and/or mushroom extracts as dietary supplements based on theories that they enhance immune function and promote health. Endobiotic (endophytic) fungi are micro fungi that host plant tissue intercellular and/or intracellular without any apparent pathological symptoms (Wilson 1995; Das and Varma 2009). To be able to sustain steady symbiosis, endophytes develop chemical substances that enhance the development of plants and benefit them to acclimatize better to the harsh environment (Gouda et al. 2016). As a treasure mine of bioactive metabolites, endophytic fungi are considered a sustainable source of various natural products, namely, quinones, saponins, alkaloids, steroids, phenolic acids, terpenoids, and tannins that exhibit antimicrobial and anticancer properties (Verma et al. 2009). In the last decade, a "bioprospecting" term was applied to refer to an old practice for searching useful bioactive compounds and other potentially valuable biochemical products from nature (Abdel-Azeem and Salem 2012).

Filamentous fungi create a wide extent of low molecular mass natural products (NPs) often related to unique bioactive properties. Prominent among these fungal secondary metabolites (SMs) and Primary metabolites (PMs) are compounds beneficial to human like antibiotics, antioxidants, fragrances or pharmaceuticals, pigments (Demain 2014). Fungal (SMs) are principally categorized as polyketides, terpenoids, alkaloids, or small non-ribosomal peptides (Keller et al. 2005). Later advances in large-scale DNA sequencing from a wide range of filamentous fungi have led to the discovery that fungal genomes possessing a broad genetic potential to produce (SMs). A remarkably large number of enzymes that produce (SMs) as non-ribosomal peptide synthases (NRPSs), and terpene synthases (TSs) has been described often as part of biosynthetic gene clusters predicted to be responsible for the synthesis of one or more NPs (Keller et al. 2017).

2.5.1 Fungal Communication as an Inducer of Silent Secondary Metabolite

Fungi and their SMs are known as one of the potential resources for novel drugs. Fungi form diverse multispecies communities within the natural habitat. They are subjected to intra- and interspecies interactions, which may result in beneficial or even harmful outputs for the species included. The real triggers leading to the activation of natural product biosynthesis in these communities are as diverse as the products themselves. They range from environmental signals, such as pH, carbon, and nitrogen sources, to organisms living in the same habitat (Yu and Keller 2005).

2.5.2 Wild Mushroom as Treasure of Natural Antioxidant

Ferreira et al. (2009) has proposed that the sensitivity of species to free radicals has contributed to the creation of endogenous defense mechanisms to eradicate them. These defenses were the response of transformation to the inevitable ramification of ROS production under aerobic conditions. Natural products with antioxidant activity can be beneficial to the endogenous defense system. In this context, the antioxidants present in the diet assume significant importance as a potential preventive agent to mitigate oxidative damage. In particular, the antioxidant properties of wild mushrooms have been studied widely and many antioxidant compounds isolated from these sources have been established so far in mushrooms.

In addition to the mechanism of action involved in their antioxidant properties, wild mushrooms can be used directly in diet to improve health, reaping the benefits of the additive and synergistic effects of both bioactive compounds. Mushrooms have become desirable as functional foods and as a source of physiologically advantageous medicines (Chang 1996). Such benefits of using mushrooms over plants as bioactive compound sources are that sometimes the fruiting body can be generated in far less time, the mycelium can also be produced swiftly in liquid culture, and the culture medium can be modified to generate optimum active product amounts as well. Many wild mushroom species had antioxidant activity, primarily associated with their phenolic content (Soares et al. 2009). Mushroom antioxidants are predominantly phenolic compounds (phenolic acids and flavonoids) accompanied by tocopherols, ascorbic acid, and carotenoids. These molecules were quantified mainly from India, Korea, Finland, Poland, Portugal, Taiwan, and Turkey in tens of different species (Table 2.1) These values are valuable in the literature but differently expressed in basis (fresh weight and dry weight extract). India's *Helvella crispa* reported the highest content of phenolic compounds produced per g of extract (34.65 mg/g), while Korea's *Sparassis crispa* reported the lowest dry-weight value (0.76 mg/g). The richest species in tocopherols were *Auricularia fuscosuccinea* (white) from Taiwan (32.46 mg/g extract), *Agaricus silvaticus* (3.23×10^{-3} mg/g dry weight), and *Ramaria botrytis* (2.50×10^{-4} mg/g fresh weight) from Portugal. The highest concentrations of ascorbic acid were found in *Auricularia fuscosuccinea* from Taiwan (11.24 mg/g extract), *Suillus collinitus* from Portugal (3.79 mg/g dry weight), and *Agaricus bisporus* from Poland (0.22 mg/g fresh weight). *Lactarius deliciosus* from Portugal presented the highest contents in β-carotene (0.09 mg/g of extract). The literature includes a few studies concerning the study of the phenolic components of wild mushrooms. High-performance liquid chromatography coupled with photodiode array detector (HPLC-DAD) (Puttaraju et al. 2006; Ribeiro et al. 2006, 2007; Kim et al. 2008; Valentão et al. 2005; Barros et al. 2008), or an ultraviolet detector (Jayakumar et al. 2009), or gas chromatography-mass spectrometry selected ion monitoring (GC-MS SIM) (Mattila et al. 2001).

Tocopherol: Some reports have been published on the tocopherols content of mushrooms. All reported the same methodology including saponification in the extraction process and analysis by HPLC coupled to UV detector. Only Barros et al. (2008) described an extraction process without saponification, adding an antioxidant to avoid tocopherols oxidation, using special precautions to protect the samples from light and heat. Ascorbic acid can also be extracted from many wild mushroom species using HPLC coupled to UV or fluorescence detector or by the spectrophotometer. Carotenoids are nature's most extensive pigments and have also received substantial attention because of both their provitamin and antioxidant roles. Particularly, β-carotene was found in several mushroom species. Carotenoids are synthesized by plants and microorganisms but not animals. Fruits and vegetables constitute the major sources of carotenoids in the human diet. Close to 90% of the carotenoids in the diet and human body are represented by β-carotene, α-carotene, lycopene, lutein, and β-cryptoxanthin (Ferreira et al. 2009).

Table 2.1 Antioxidants quantified from wild mushrooms

Mushroom species	Phenolic compounds	Tocopherols	Ascorbic acid	β-Carotene	Country
Agaricus arvensis	0.17[a]	1.22×10^{-3}[a]	0.02[c]	8.52×10^{-3}[c]	Portugal
Agaricus bisporus (white)	4.32×10^{-3}[a]	–	0.17[a]	–	Finland
Agaricus bisporus (brown)	4.69×10^{-3}[a]	–	0.21[a]	–	Finland
Agaricus bisporus	0.54[a]	–	–	–	Korea
Agaricus bisporus	–	–	0.22[b]	–	Poland
Agaricus bisporus	0.03[a]	2.41×10^{-3}[a]	0.03[c]	1.95×10^{-3}[c]	Portugal
Agaricus bisporus	–	9.20[c]	–	0.04[c]	Turkey
Agaricus blazei	0.70[a]	–	–	–	Korea
Agaricus blazei	–	5.44[c]	–	–	Taiwan
Agaricus romagnesii	0.08[a]	1.29×10^{-3}[a]	0.04[c]	1.32×10^{-3}[c]	Portugal
Agaricus silvaticus	–	3.23×10^{-3}[a]	0.04[c]	5.42×10^{-3}[c]	Portugal
Agaricus silvicola	0.35[a]	1.17×10^{-3}[a]	0.04[c]	3.02×10^{-3}[c]	Portugal
Agrocybe cylindracea	–	5.27[c]	–	–	Taiwan
Amanita caesarea	–	–	2.07[a]	–	Portugal
Amanita rubescens	0.49[a]	–	0.03[a]	–	Portugal
Auricularia mesenterica	–	9.45[c]	1.63[c]	–	Taiwan
Auricularia fuscosuccinea (brown)	–	12.69[c]	11.24[c]	–	Taiwan
Auricularia fuscosuccinea (white)	–	32.46[c]	7.99[c]	–	Taiwan
Auricularia polytricha	3.17[c]	–	–	–	India
Auricularia polytricha	–	23.61[c]	3.28[c]	–	Taiwan
Boletus badius	–	8.80[c]	–	–	Turkey
Boletus edulis	10.19[c]	–	–	–	India
Boletus edulis	–	3.30×10^{-4}[a]	–	2.73×10^{-3}[c]	Portugal
Boletus edulis	–	6.18[c]	–	–	Taiwan
Calocybe gambosa	–	4.00×10^{-4}[a]	0.40[c]	6.41×10^{-3}[c]	Portugal
Calvatia gigantea	–	–	0.15[a]	–	India
Cantharelus cibarius	2.00[c]	3.00×10^{-5}[a]	0.42[a]	–	India
Cantharelus cibarius	7.80×10^{-3} to 2.54×10^{-2}[a]	1.50×10^{-4}[a]	0.48[c]	0.01[c]	Portugal
Cantherallus clavatus	13.22[c]	–	–	–	India
Clavulina cinerea	–	–	0.42[a]	–	India
Craterellus cornucopioides	–	1.87×10^{-3}[a]	0.87[c]	0.01[c]	Portugal
Fistulina hepatica	0.37–0.55[a]	–	2.80[a]	–	Portugal
Flammulina velutipes	0.17[a]	–	–	–	Korea
Ganoderma lucidum	0.16[a]	–	–	–	Korea
Ganoderma lucidum	–	1.19[c]	–	–	Taiwan
Ganoderma tsugae	–	1.07[c]	–	–	Taiwan

(continued)

Table 2.1 (continued)

Mushroom species	Phenolic compounds	Tocopherols	Ascorbic acid	β-Carotene	Country
Geastrum arenarius	4.80[c]	–	–	–	India
Gomphus floccosus	–	–	0.26[a]	–	India
Grifola frondosa	–	0.05, 0.11[c]	0.05, 0.14[c]	–	Taiwan
Helvella crispa	34.65[c]	–	–	–	India
Hericium erinaceus	–	0.06[c]	–	–	Taiwan

Source: Ferreira et al. (2009)

2.5.3 Ganoderma lucidum *A Treasure Trove of Antioxidant*

Ganoderma lucidum (aphyllophoromycetideae from the family Polyporaceae) is a mushroom that has been utilized in customary Chinese medication for a long time. Likewise, *G. lucidum* has been accounted for as a significant wellspring of bioactive compounds, for example, polysaccharides, triterpenoids, and proteins, which are utilized to avert or treat different human diseases, for example, malignancy, immunological issues, neurodegenerative infections, hepatitis, hypertension, ceaseless bronchitis, bronchial asthma, and so on.

Past investigations have detailed that *G. lucidum* performs antioxidant agent, hypoglycemic, antitumor, and immunomodulatory. Also, *G. lucidum* acts to lessen oxidative pressure and advance neuroprotective impacts, prompting neuronal separation and securing against cerebral ischemic injury by hindering apoptosis. Also, *G. lucidum* extract lessens the statements of proinflammatory and cytotoxic elements from the initiated microglia and viably secures the dopaminergic neurons against incendiary and oxidative harm. Zhang et al. (2006) recommended that *G. lucidum* jams the harmed spinal engine neuron articulation levels of the proteins that assume significant jobs in axonal regeneration. These outcomes infer that the polysaccharide disengaged from *G. lucidum* have neural protection and antioxidant properties (Lacin et al. 2019).

An assortment of polysaccharides and triterpenoids developed in many biological activities, for example, *G. lucidum*. The cell dividers of *G. lucidum* spores contain a high number of polysaccharides. An assortment of bioactive polysaccharides segregated from *G. lucidum* has been seen as β-1,3-glucans polysaccharide peptides like peptidoglycan, which interface with the immune system. A few water-soluble polysaccharides have been fractionated and cleaned from the aqueous extraction of *G. lucidum*. More than 140 triterpenoid mixes were found in *G. lucidum*, which can be separated into *Ganoderma* alcohols or *Ganoderma* acids. Some triterpene-rich extracts of *G. lucidum* contain high amounts of lucidenic acids, which can be purified from the extract, and exert immunostimulatory activities. Several nucleotides and nucleobases were qualitatively identified in the mushroom samples. Some investigations show that *G. lucidum* extract elevates the activity of super oxide dismutase and catalase enzymes associated with wiping out harming responsive oxygen reactive species. Zhu et al. (1999) studied the antioxidant activity of *G. lucidum* mix in vitro. *Ganoderma* crude extract was exposed to boiling water media, then the aqueous extract was separated. Polysaccharide and terpene fractions have been achieved. Both of the fractions were analyzed for their antioxidant activity.

It has been demonstrated that the terpene fraction showed the highest antioxidant activity. In that fraction, ganoderic acids A, B, C, and D, lucidenic acid B reported the highest antioxidant activity (Zhu et al. 1999).

Heleno et al. (2013) concluded that extracts obtained from *G. lucidum* grown on germinated brown rice (GLBR) show important antioxidant activity against several in vitro antioxidant systems. Consumption of GLBR extract could distinctly expand the activity of enzymes like superoxide dismutase, glutathioneperoxidase, and catalase in the sera, liver, and brain of mice (Hasnat et al. 2013).

Ganoderma polysaccharides have been determining their activity as antioxidants by different strategies. Entire polysaccharides complex affirmed the competent radical scavenging capacities. Notwithstanding the extraordinary antioxidants capability of homo-glucans and hetero-glucans from this *G. lucidum* and their mechanism of action have not yet been clarified. Molecular mass, chemical composition, type of glycosidic linkage, and conformation are the fundamental variables influencing the bioactivity of polysaccharides. Among them, the molecular weight was one of the most significant structural features of polysaccharides, as it is identified with the quantity of reductive hydroxyl group terminals (on a per unit mass basis) liable for accepting and wiping reactive oxygen species. Low molecular weight polysaccharides subsequently have relatively higher antioxidant ability (*Ganoderma lucidum* polysaccharides1 GLPL1and *Ganoderma lucidum* polysaccharides2 GLPL2) (Wang et al. 2017).

The scavenging impact against superoxide radicals of low molecular weight chitosan (9 kDa) was more powerful than high molecular weight chitosan (760 kDa) (Xing et al. 2005). Structural analyzes of *G. lucidum* polysaccharides (GL-PSs) show that GL-PSs are heteropolymers, in which glucose is the utmost sugar component, while mannose, galactose xylose, and fucose are present in lower amounts (Wachtel-Galor et al. 2011). Polysaccharides isolated from the fruit bodies of *G. linghzi* indicated also potential antioxidant activity (Zhu et al. 2013). Additionally, Kao et al. (2013) record that β-1,3-glucan (a low-molecular weight glucan) isolated from *G. lucidum* was skillful to elevate (from 40% to 80%) the feasibility of a mouse leukemic monocyte macrophage cell line (RAW 264.7) with H_2O_2—hydrogen peroxide free radical induced oxidative stress, and decrease reactive oxygen species (ROS) formation. It also terminated the activities of neutral and acidic sphingomyelinases (SMases). Mannose-based homo-polysaccharide was able to increase the activity of antioxidant enzymes. Moreover, the antioxidant capability of high-purity polysaccharides, many researches focused on the high radical scavenging impact of polysaccharide conjugates such as polysaccharide-protein complexes and polyphenolic-associated polysaccharides, polysaccharide chelating metal, metal ion-enriched polysaccharides, and polysaccharide mixtures (Wang et al. 2017).

The protein or peptide moiety in polysaccharides and the scavenging effect on superoxide and hydroxyl radicals are elucidated by (Liu et al. 2007) Polysaccharide-protein complexes extracted from *G. lucidum* with lower polysaccharide/protein ratios were more fruitful in the scavenging function. Further investigations indicated that, besides the quantity of peptide or protein molecules, their composition has to be considerable Amino acids, such as tryptophan tyrosine, methionine, lysins, histidine, and tyrosine, are able to donate protons to electron-deficient radicals. The most common polysaccharide isolated from *G. lucidum*, GLP, consists of 14 amino acids. Several polysaccharides (D-rhamnose, D-fructose, D-galactose, D-mannose, D-xylose, and D-glucose) are present as sugars. The molecule has a great potentiality to increase antioxidants, serum insulin levels, and diminish lipid peroxidation. The survival rate of macrophages, and securing the mitochondria against injury by a membrane-permeant oxidant (t-BOOH), which has also demonstrated the high antioxidant activity (Jiang et al. 2012).

Another approach to influencing the antioxidant activity of polysaccharides is a chemical modification by moderating the solubility of water-insoluble polysaccharides. Chen et al. (2005) reported that *G. lucidum* polysaccharides could highly improve antioxidant enzyme activities. Moreover, Liu et al. (2007) recorded that sulfation strongly improved the water solubility and bile acid-binding abilities of a water-insoluble polysaccharide from *G. lucidum* (GLP) (Fig. 2.6).

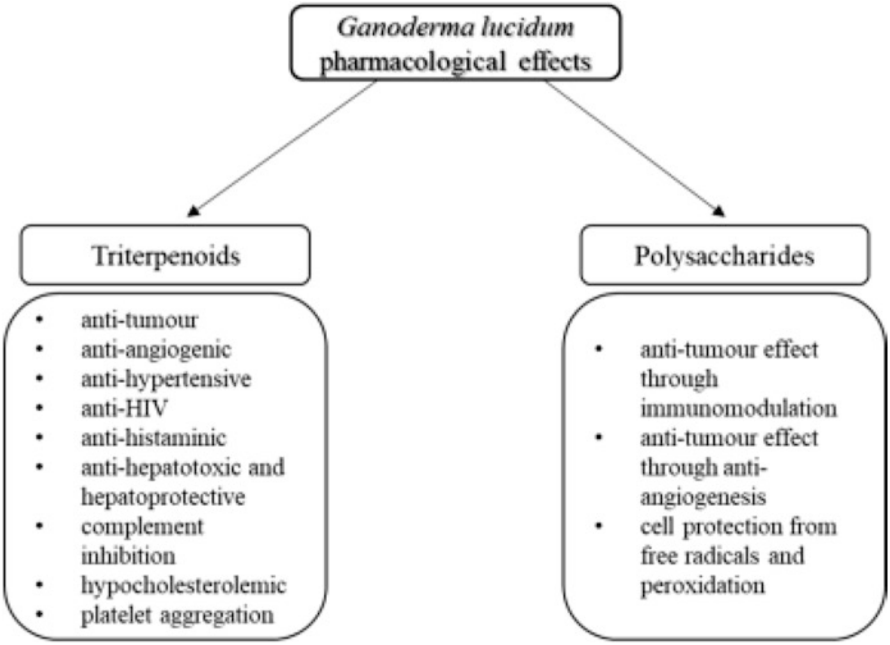

Fig. 2.6 *Ganoderma lucidum* pharmacological effects related to the specific group of biological compounds (Boh et al. 2007)

2.5.4 Glutathione, Altruistic Metabolite in Filamentous Fungi and Yeast

Baker's yeast *Saccharomyces cerevisiae* have represented as a biological model system that assisted the unraveling of the role of glutathione in cellular processes. Glutathione was first termed as "philothion" by Rey-Pahlade over 120 years earlier, as a substance that appropriates to reduce elemental sulfur discharging hydrogen sulfide (Meister 1988). This "sulfur-loving" compound was isolated by the English biochemist Frederic Gowland Hopkins and renamed glutathione. Regarding chemistry, glutathione (GSH) was base as a thiol tripeptide with unusual γ-glutamyl linkage (γ-L-glutamyl-Lcysteinyl glycine). Research on the character and function of GSH in animals over the last 40 years have been active and enriched by Alton Meister and his colleagues (Meister and Anderson 1983) Most research concerned with animal GSH is multidisciplinary, comprising biochemical, toxicological, physiological, and clinical aspects of its biological function. In comparison with the biology of GSH in microbial systems has received less publicity, even though it is generally accepted that GSH is physiologically relevant nonprotein thiol (NPT) present in most microorganisms. GSH can make up about 1% of the cellular dry weight in many types of human and animal cells so glutathione is way significant and abundant molecular (Penninckx and Elskens 1993) researches typically concentrate on biochemical "in vivo" Studies, and the metabolism of GSH was investigated as a significant component in cellular processes a (Fig. 2.7).

GSH is a significant multifaceted cellular metabolite in Fungi. Its clear cooperation in the response of suffering cells subjected to stress places GSH in the category of altruistic compounds. The most particular physiological roles of GSH relate to the state of stress. For microorganisms, stress means the response to a chronic or sudden experience of different harmful circumstances like heat, cold, osmotic shock, starvation, alterations in the pH, water potential, or exposure to radiation. These situations, however, refer to cultures grown in laboratory media, which scarcely represent the most desirable ecological state or even may hide unexpected development of stress, for example, the presence of harmful metabolic by-products normally created by general carbon and/or nitrogen cellular metabolism. In this case, GSH plays a significant role. The role of GSH is not limited to excessively stressful conditions at all. A cell completely deprived of GSH is unable to function even under conditions free of stress. One of the main roles of GSH is related to the maintenance of cellular integrity, in particular to the membrane structures, as well as to cellular differentiation and development. To accomplish this essential role, the fungal cell does not need necessarily to use its full potential for the synthesis of GSH; often only a few amounts of the thiol are sufficient.

There are several important enzyme systems accompanied by GSH. However, the chemical reactivity of the tripeptide, which modulates its effect in the cellular

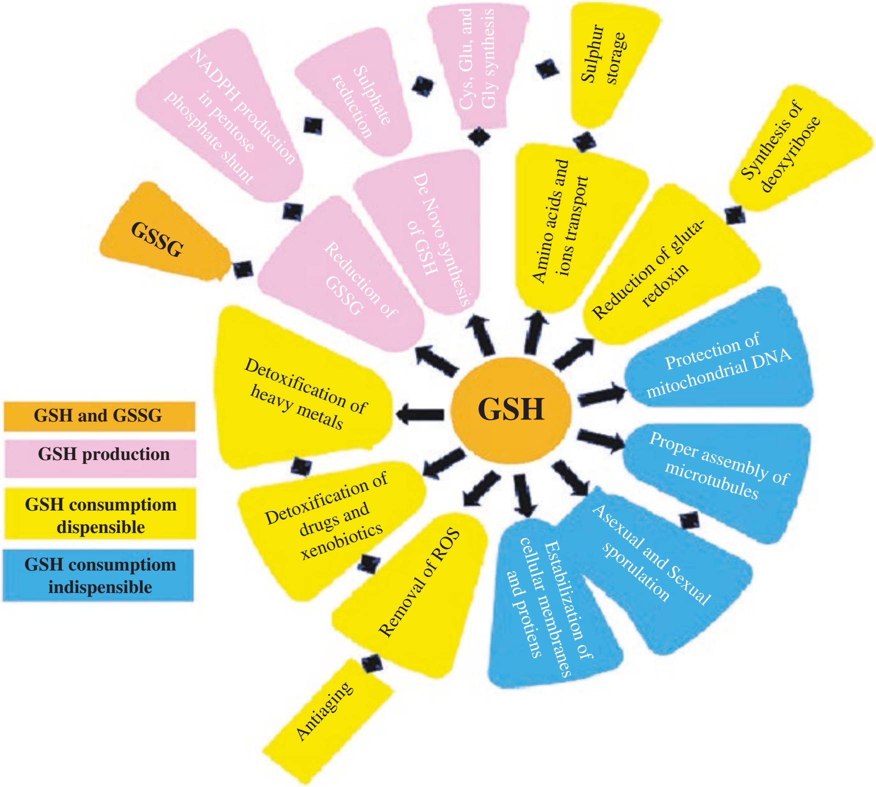

Fig. 2.7 GSH production and consumption machines in the metabolic network of fungi (Pocsi et al. 2004)

redox cycle, should not be ignored! Undoubtedly, this is one of the most significant aspects that demonstrate the usefulness of this compound. So, we must emphasize the deep influence exerted by investigators of mammalian physiology, on the development of GSH research. Research on GSH in microorganisms, particularly in fungi, has exploded in the last 10 years. This can be attributed in part to the enthusiasm of investigators working in very different fields, for example, plant and animal physiology, to use microbial model organisms, particularly yeasts (Pocsi et al. 2004). A brilliant study in 2009 investigated that *Aspergillus nidulansis fungus specific gulthion transferase* (Sato et al. 2009). Finally, in addition to glutathione, several glutathione analogs and precursors are also commercially important, most of the analogs are produced by synthetic chemistry, but extraction of glutathione itself from potential and sustainable sources, like yeast and fungi needs to be investigated with greater intensity.

2.5.5 Micro Fungi as Source of Antioxidants

2.5.5.1 *Sanghuangporus sanghuang*

Sanghuangporus sanghuang, as a new species has been discovered that only grows on living mulberry trees. Studies on *Sanghuang* showed that its main components are polysaccharides, flavonoids, and triterpenoids. Triterpenoids are a class of bioactive substances in medicinal fungi, but their antitumor and antioxidant properties have been less studied than those of polysaccharides. They have many functions, such as inhibiting histamine release, lowering blood pressure, and protecting the liver.

The first use of the medicinal fungus *Sanghuang* can be traced back to 2000 years ago in China. According to The Theory of Medicinal, *Sanghuangporus sanghuang* tastes bitter and is used as a traditional Chinese medicine for the treatment of diarrhea, night sweats, metrorrhagia, drench, and stomach pain, prolapse of spilled blood, leucorrhea, and amenorrhoea. *Shennong's* Herbal Classic of Materia Medica stated that long-term use of *Sanghuangporus sanghuang* can prolong life, detoxify, and improve digestion.

To maximize the yield of the antioxidants and active ingredients such as the triterpenoids from authentic *Sanghuangporus sanghuang*. Cai et al. (2019) examined four parameters of the extraction process, including the extraction time, solid–liquid ratio, extraction temperature, and ethanol concentration to optimize the triterpenoid extraction processes of *Sanghuangporus sanghuang* mycelium. The results showed that the optimum conditions of ultrasonic extraction required an 80% ethanol concentration, a 1:20 solid–liquid ratio, a 20-min extraction time, and a 60 °C extraction temperature, to obtain a maximum triterpenoid extraction of 13.30 mg/g. Antioxidant capacity tests showed that the *Sanghuangporus sanghuang* triterpenoids had high clearance capabilities for hydroxyl free radicals, superoxide anions, 2,2-diphenyl-1-picrylhydrazyl free radicals, and 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulfonate) radicals, indicating that the *Sanghuangporus sanghuang* triterpenoids had high antioxidant activities.

In 1968, Ikekawa et al. (1968) found that the sarcoma cell line S-180 was inhibited by 96.7% in mice when treated with a water extract of the *Sanghuang* fruiting body. The medicinal functions of *Sanghuang* have since been studied by many researchers, who have characterized its antitumor and antioxidant properties. *Sanghuang* is considered one of the most effective anticancer drugs found in higher fungi and has been extensively studied as a medicinal fungus.

2.5.5.2 *Cerrena unicolor*

Investigation and isolation of new natural bioactive substances are important for the food industry due to the growing importance of their antioxidative activity, which is crucial in food preservation processes. Unfortunately, the commonly used synthetic substances such as hydroxyanisole (BHA) and hydroxytoluene (BHT) are likely to be toxic for living organisms. Interestingly, the physiological life cycle of the white rot *Basidiomycota* is associated with a relatively high concentration of ROS, which might initiate the secondary wood cell wall decay processes. Therefore, these organisms also possess a very efficient antioxidative system consisting of enzymatic (peroxidases, laccase, catalase, and superoxide dismutase) and nonenzymatic elements (phenolic derivatives or polysaccharides). It is known that, besides the polysaccharides, fungi can produce many secondary metabolites with antioxidative activities including a number of phenolic compounds (e.g., hispidin and its dimmers or fungal pigments usually isolated from fruiting bodies) (Jaszek et al. 2013).

Three bioactive fractions, extracellular laccase (ex-LAC), crude endopolysaccharides (c-EPL), and a low molecular subfraction of secondary metabolites (ex-LMS), were isolated from the idiophasic cultures of the white rot fungus *Cerrena unicolor*. The highest reducing capability was found for the ex-LMS 800 μg/mL. A very high prooxidative potential was observed for the ex-LAC probes. They showed antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* (Jaszek et al. 2013).

2.5.5.3 *Mucor circinelloides*

Molecular screening methods claimed there are as many as 5.1 million species of fungi, of which only approximately 100,000 have been reported in the literature. Among these fungi, 14,000 species are mushrooms, 5000 are macro fungi, and more than 1800 fungi have been identified as possessing pharmacological, therapeutic, and medicinal features. The pathogenicity of Mucorales is largely believed to be due to endocellular excretions and the production of subtilisins, chitinases, proteinases, and antioxidant proteins (e.g., superoxide dismutase, catalase, and peroxidase). From an industrial point of view, the class Zygomycetes of Zygomycota is more important than its second class Trichomycetes because of its two widely used bioactive compound producing genera: Mucor and Rhizopus. Zygomycetes can produce a wide range of metabolites including enzymes, lipids, ethanol, organic acids, food colorants, amino acids, chitosan, chitin, and proteins.

Genus *Rhizopus*, specifically, has been majorly exploited to produce lactic acid, fumaric acid, amylases, pectinases, steroids, lipases, ureases, and tannases, whereas genus *Mucor* is considered a good source for cellulases, phytases, proteases, ethanol, lipids, and food colorants. Due to the large storage capability of these metabolites in their mycelium/biomass, as well as their nutritional and pharmaceutical importance, there is an increasing interest in utilizing the biomass of zygomycetes as a source of microbial proteins, microbial lipids, microbial ethanol, microbial food colorants, and microbial bioactive components such as essential amino acids, antibiotics and chitosan in food, aquaculture feed, and pharmaceutical industries. Mucor and Rhizopus can be a great source of natural antioxidants and these natural antioxidants can be termed as “microbial antioxidants”.

Mucor circinelloides strains belong to the family Mucoraceae, order Mucorales, subclass Incertaesedis, and class Zygomycetes. These strains are excellent producers of carotene, lycopene, lipids, and bioactive component, for example, Linolenic acid (GLA), and are also easy to handle and produce with the availability of molecular and transformation tools and genome sequence features. Phenolic compounds were detected, especially tannins and flavonoids. Total phenol content was attributed to overall antioxidant capacity. Submerged fermentation with nutritional stress conditions was found to be an excellent way of producing surplus amounts of natural antioxidants/secondary metabolites with their vast potential commercial application in food and pharmaceutical industries from these fungi (Hameed et al. 2017).

2.6 Why Do Plants Synthesize Antioxidants?

Plants have been the vital sources of natural products since the starting of investigation, and it may too be expressed that they are the natural skilled workers of molecules created in infinite orders. Since plants are seated organisms, they experience a number of changes to adjust stress conditions. These changes happen due to the formation of different significant compounds. These compounds are valuable resources of plants since they keep up their age and health. Endophytes and plants have a symbiotic relationship, where the endophytes obtain benefits in the form of nutrition, and in return, synthesize specific compounds that assist the plant in metabolism and protection from stressful conditions. These compounds produced by the endophytes present a hidden range of known and unknown medicinal significance (Darwish et al. 2020). Gave the concept of horizontal gene transfer that reveals that endophytes and the host plant collaborate to the production of bioactive molecules. Some endophytes have been predominating biosynthetic capabilities, owing to their likely gene recombination with the host while dwelling and reproducing inside the healthy plant tissues (Li et al. 2005). Taxol, jesterone, torreyanicacid, pestaloside, ambuic acid, pestalotiopsins, and 2-a-hydroxydimeniol are few examples of such compounds (Strobel and Daisy 2003). These bioactive molecules synthesized by plants can be utilized for the treatment of human diseases. Apart from plants, endophytes, which are in a symbiotic relationship with the plants, are also considered to be a vital source of antioxidants (Huang et al. 2007).

2.6.1 Endophytic Fungi as a Natural Source of Antioxidants

As all higher plants are hosts to one or more endophytic microbe on this earth. Endophytic fungi are microbes that reside in living plant tissues without causing any immediate harm to their host. They are highly diverse microorganisms that are chemical synthesizers inside host plants. Most antioxidants known today are industrially synthesized although being accounted for causing liver damage and carcinogenesis. In contrast, natural-derived antioxidants, like those produced by endophytes, have not been found to be harmful. Endophytes have the ability to use several substrates, producing a wide array of secondary metabolites. These comprise a large but little explored proportion of fungal diversity. Paclitaxel, a potent anticancer agent isolated from endophytic fungi such as *Taxomyces andreanae* and *Pestalotia* spp., so, endophytes have been recognized as potential new sources of anticancer, antimicrobial, and antimalarial bioactive metabolites, attracting much more attention from researchers. These metabolites include steroids, xanthines, phenols, isocoumarins, quinones, and terpenoids (Caicedo et al. 2019). Fusaria both positively and negatively affect crop cultivation: the harmful effects of pathogens and toxin producers and the beneficial effects of the biological control agents, which can be used as microbial pesticides, are easily understood. In contrast, the effects and potential of endophytes on crop cultivation are poorly understood. Although most endophytes are thought to be nonpathogenic further analyzes of the ecological functions of *Fusarium* endophytes are needed to elucidate their roles in crop cultivation (Imazaki and Kadota 2015).

Several studies have shown that extracellular polysaccharides of endophytic fungi present antioxidant activity (Yadav et al. 2014; Caicedo et al. 2019). Caicedo et al. (2019) reported high antioxidant potential of *Fusarium oxysporum* endophytic fungus isolated from the leaves of *Otoba gracilipes*, a medicinal tree from a tropical rainforest in Colombia.

Chaetomium globosum CDW7, an endophyte from *Ginkgo biloba*, exhibited strong inhibitory antifungal activity against phytopathogens such as *Fusarium graminearum*, *Rhizoctonia solani*, *Magnaporthe grisea*, *Pythium ultimum*, and *Sclerotinia sclerotiorum* both in vitro and in vivo. Extract from *C. globosum* CDW7, which had been deposited in the China General Microbiological Culture Collection Center (CGMCC) with an accession number 6658, has the strongest antioxidant activity among the studied endophytic fungi from *G. biloba* comparable to those of vitamin C and trolox, the well-known antioxidants. *Chaetomium globosum* and *C. cochlioides* are antagonistic to species of *Fusarium* and *Helminthosporium*. Flavipin is considered the major antioxidant component of CDW7's metabolites; it reacts by donating its electrons to the free radicals, leading to SOD and GSH-Px activity improvement and suppression of MDA content. Chaetopyranin also showed antioxidant activity. The azaphilone compounds are produced by different *Chaetomium* species, which display various biological activities such as antioxidant, nematicidal, antimicrobial, antifungal, anticancer, and inflammatory activities. Endophytic fungus *Chaetomium globosum* INFU/Hp/KF/34B isolated from *Hypericum perforatum* has been shown to produce hypericin and emodin of high medicinal value as antioxidants. *C. cupreum* can be a new source of natural antioxidants useful for industrial applications (Darwish et al. 2020).

Yadav et al. (2014) reported the presence of alkaloids, phenols, flavonoids, saponins, and terpenes in 21 endophytic fungi isolated from *Eugenia jambolana*, which can be a potential source of novel natural antioxidant compounds. A significant positive correlation was found between antioxidant activity and TPC in fungal extracts. There are 36% of endophytic extracts having high phenolic content exhibited potent antioxidant activity. *Chaetomium* sp., *Aspergillus* sp., *Aspergillus peyronelii*, and *Aspergillus niger* strains showed the highest antioxidant activity ranging from 50% to 80% having 58 to 60 mg/g GAE total phenolics. In their work, Darwish et al. (2020) collected all available data concerning antioxidants produced by endophytic Chaetomium. These are explained in the following paragraphs.

2.6.1.1 Flavipin

Flavipin is a well-known natural product that is isolated from endophytes belonging to *Chaetomium* sp. associated with leaves of *Ginkgo biloba* (Ye et al. 2013). Yan et al. (2018) succeeded in isolating bioactive metabolites with antifungal activities from this fungus; the metabolites are flavipin, chaetoglobosins A and D, chaetoglobosins R (4) and T (5), new isocoumarin derivative prochaetoviridin A (1), new indole alkaloid, and chaetoindolin A (2) and chaetoviridin A (3). Flavipin is considered the major antioxidant component of CDW7's metabolites; it reacts by donating its electrons to the free radicals, leading to SOD and GSH-Px activity improvement and suppression of MDA content. This metabolite possesses three phenolic hydroxyl and two aldehyde groups, which are characteristic functional groups with antioxidant activity. When cultured under the optimal condition (25 °C, 100/250 mL flask, 12 discs/flask, 150 rpm, pH 6.5) for 14 days, *Chaetomium globosum* CDW7 was a highly yielded bio-source of antioxidant Flavipin synthesizing a remarkable production of 315.5 mg/L (Ye et al. 2013).

Another endophytic fungus from *Ginkgo biloba*, *Chaetomium* sp. NJZTP21 (GenBank accession number: JN588553), isolated from the healthy leaf of the plant was able to produce Flavipin, which significantly inhibited the growth of several plant pathogenic fungi, especially *Fusarium graminearum*. But the extract from *C. globosum* CDW7, which had been deposited in the China General Microbiological Culture Collection Center (CGMCC) with an accession number 6658, has the strongest antioxidant activity among the studied endophytic fungi from *G. biloba* comparable to those of vitamin C and trolox, the well-known antioxidants (Ye et al. 2013). *Chaetomium globosum* and *C. cochlioides* are antagonistic to species of *Fusarium* and *Helminthosporium*. They exhibited good control over many plant pathogens; seed coating treatments with viable spores of *Chaetomium globosum* were found to exert antagonistic effect controlled *Fusarium roseum* f. sp. *cerealis* "graminearum" in corn; reduced disease incidence of apple scab caused by *Venturia inequalis*; suppressed damping-off of sugar beet caused by *Pythium ultimum*; had an antagonistic effect against *Macrophomina phaseolina*, *Pythium ultimum*, *Bipolaris sorokiniana*, *Rhizoctonia solani*, and *Alternaria brassicicola*; and reduced the quantity of sporulation of *Botrytis cinerea* on dead lily leaves exposed in the field (Biswas et al. 2012; Shternshis et al. 2005).

2.6.1.2 Chaetopyranin

The basic structure of chaetopyranin (I) is chromenol (I) (chromene carrying one or more hydroxyl substituents). It is chemically known as 3,4-dihydro-2*H*-chromene substituted by a hydroxyl group at position 6, a 3-hydroxybut-1-en-1-yl at position 2, a formyl group at position 5, and a prenyl group at position 7 (Wang et al. 2006). These two compounds have been isolated from an endophytic fungus *Chaetomium globosum*, associated with *Polysiphonia urceolata*, and are found to possess antioxidant activity. The former compound also exhibits anticancer activity (Wang et al. 2006). Chaetopyranin also showed antioxidant activity.

2.6.1.3 Azaphilone

The most remarkable and valuable properties of azaphilones include their natural origin, yellow-red spectra, thermostability (in comparison with other natural red pigments), and water solubility. The azaphilone compounds produced by different *Chaetomium* species display various biological activities such as antioxidant, nematicidal, antimicrobial, antifungal, anticancer, and inflammatory activities (Borges et al. 2011).

2.6.1.4 Hypericin and Emodin

Endophytic fungus *Chaetomium globosum* INFU/Hp/KF/34B isolated from *Hypericum perforatum* has been shown to produce hypericin and emodin of high medicinal value as antioxidants. This endophytic fungus has significant scientific and industrial potential to meet the pharmaceutical demands in a cost-effective, easily accessible, and reproducible way (Kusari et al. 2008; Zhao et al. 2011).

2.6.1.5 Mollicellins

Mollicellins O (1) isolated from the endophytic fungus *Chaetomium* sp., Eef-10, which was isolated from *Eucalyptus exserta* by Ouyang et al. (2018), showed antioxidant activity based on DPPH radical scavenging. For more details concerning antioxidants producing fungi in Egypt please check Abdel-Azeem et al. (2018) and Abo Nahas (2019).

2.7 Fungal Antioxidants: Extraction, Estimation, and Biological Assay

The field of free radical chemistry is gaining more attention these days. Free radicals are reactive oxygen and nitrogen species that are generated by various physiological processes in the body. Uncontrolled generation of free radicals leads to attack on membrane lipids, proteins, enzymes, and DNA causing oxidative stress and ultimately cell death. These ROS are responsible for many degenerative human diseases like diabetes mellitus, cancer, neurodegenerative disorders, Alzheimer's disease, Parkinson's disease, atherosclerosis, aging, and inflammatory diseases (Yadav et al. 2014).

Carbohydrate antioxidants are expected to have better applicability as they are easily isolated, purified, water-soluble, and have fewer chances of toxicity towards the cell. Fungal EPSs have several applications in the food, feed, cosmetic, medicine, and pharmaceutical industries. The activities of fungal carbohydrate compounds are dependent on different content and arrangements during the polymerization of its building unit, monosaccharides.

Their composition varies from pure sugars to sugars combined with a second unit such as protein, phosphate, sulfate, or amine. Different types of sugar units were found in fungal EPSs such as glucose, mannose, galactose, xylose, fucose, and rhamnose. It was also noticed that EPSs composed of the same monosaccharide units that were synthesized by different fungi had different molecular weights. This is caused by differing chain lengths or branching patterns that give polysaccharides a great diversity of structure, property, and functions. For instance, the extracellular polysaccharide produced by the mangrove-associated fungus *Fusarium oxysporum* Dzf17 is defined as galactofuranose-containing mannoglucogalactan, consisted of galactose, glucose, and mannose in a molar ratio of 1.33:1.33:1.00, and its molecular weight was about 61.2 kDa (Abdel-Azeem et al. 2019).

Fortunately, not all fungal secondary metabolites are toxic to humankind such as; antibiotics, phytotoxins, enzymes, and antioxidants, which gave great importance to fungi in industrial applications (Darwish 2019). Novel fungi that have the capability to synthesize unique polysaccharides with antioxidant properties became the scientists' target.

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