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Review Article

Microscopic Marvels: Essential Role of Fungi in Nature

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ABSTRACT

Besides plants and animals, the Fungi kingdom describes several species characterized by various forms and applications. They can be found in all habitats and play an essential role in the excellent functioning of the ecosystem, for example, as decomposers of plant material for the cycling of carbon and nutrients or as symbionts of plants. Furthermore, fungi have been used in many sectors for centuries, from producing food, beverages, and medications. Recently, they have gained significant recognition for protecting the environment, agriculture, and several industrial applications. The current article intends to review the beneficial roles of fungi used for a vast range of applications, such as the production of several enzymes and pigments, applications regarding food and pharmaceutical industries, the environment, and research domains, as well as the negative impacts of fungi (secondary metabolites production, etiological agents of diseases in plants, animals, and humans, as well as deteriogenic agents).

INTRODUCTION

Fungi are eukaryotic microorganisms. Fungi can occur as yeasts, Molds, or as a combination of both forms. Some fungi are capable of causing superficial, cutaneous, subcutaneous, systemic or allergic diseases. Yeasts are microscopic fungi consisting of solitary cells that reproduce by budding. Molds, in contrast, occur in long filaments known as hyphae, which grow by apical extension. Hyphae can be sparsely septate to regularly septate and have a variable number of nuclei. Regardless of their shape or size, fungi are all heterotrophic and digest their food externally by releasing hydrolytic enzymes into their immediate surroundings (absorptive nutrition). Other characteristics of fungi are the ability to synthesize lysine by the L-α-adipic acid biosynthetic pathway and possession of a chitinous cell wall, plasma membranes having the sterol ergosterol, 80S rRNA, and microtubules composed of tubulin. (1) Humans have been indirectly aware of fungi since the first loaf of

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leavened bread was baked and the first tub of grape must was turned into wine. Ancient peoples were familiar with the ravages of fungi in agriculture but attributed these diseases to the wrath of the gods. The Romans designated a particular deity, Robus, as the god of rust and, in an effort to appease him, organized an annual festival, the Robi Galia, in his honour. Fungi are everywhere in very large numbers—in the soil and the air, in lakes, rivers, and seas, on and within plants and animals, in food and clothing, and in the human body. Together with bacteria, fungi are responsible for breaking down organic matter and releasing carbon, oxygen, nitrogen,
and phosphorus into the soil and the atmosphere. Fungi are essential to many household and industrial processes, notably the making of bread, wine, beer, and certain cheeses. Fungi are also used as food; for example, some mushrooms, morels, and truffles are epicurean delicacies, and mycoproteins (fungal proteins), derived from the mycelia of certain species of fungi, are used to make foods that are high in protein. Studies of fungi have greatly contributed to the accumulation of fundamental knowledge in biology. For example, studies of ordinary baker's or brewer's yeast (*Saccharomyces cerevisiae*) led to discoveries of basic cellular biochemistry and metabolism. Some of these pioneering discoveries were made at the end of the 19th century and continued during the first half of the 20th century. From 1920 through the 1940s, geneticists and biochemists who studied mutants of the red bread mold, *Neurospora*, established the one-gene–one-enzyme theory, thus contributing to the foundation of modern genetics. Fungi continue to be useful for studying cell and molecular biology, genetic engineering, and other basic disciplines of biology. The medical relevance of fungi was discovered in 1928, when Scottish bacteriologist Alexander Fleming noticed the green mold *Penicillium notatum* growing in a culture dish of *Staphylococcus* bacteria. Around the spot of mold was a clear ring in which no bacteria grew. Fleming successfully isolated the substance from the mold that inhibited the growth of bacteria. In 1929 he published a scientific report announcing the discovery of penicillin, the first of a series of antibiotics—many of them derived from fungi—that have revolutionized medical practice. Another medically important fungus is *Claviceps purpurea*, which is commonly called ergot and causes a plant disease of the same name. The disease is characterized by a growth that develops on grasses, especially on rye. Ergot is a source of several chemicals used in drugs that induce labour in pregnant women and that control hemorrhage after birth. Ergot is also the source of lysergic acid, the active principle of the psychedelic drug lysergic acid diethylamide (LSD). Other species of fungi contain chemicals that are extracted and used to produce drugs known as statins, which control cholesterol levels and ward off coronary heart disease. Fungi are also used in the production of a number of organic acids, enzymes, and vitamins.(2)

Fungal Diversity and Classification

Fungi are the second most species-rich organism group after the insects; hence, it is more challenging to complete the global fungal inventory, as compared to other organisms such as plants. Fungi play key roles in ecosystems as decomposers, mutualists and pathogens, while in most cases, role of individual fungus in nature is still unknown. The increasing number of virulent infectious diseases caused by fungi is regarded as a worldwide threat to food security. An unprecedented number of diseases caused by fungi and fungal-like organisms (e.g. oomycetes) have recently resulted in some of the most severe die-offs and extinctions ever witnessed in wild species. Among these incidences, most of the pathogenic fungi were previously undescribed or very little information was available on them before the disasters occurred. Considering this, the description of all fungal species can help humankind to find, guard and prevent disasters incurred by fungal pathogens. (3) It has been estimated that all the plant, animal or microbial species would be described in about 30–90 years before they become extinct, considering that there are probably 1.5–3 million undescribed species on the earth with an extinction rates of 0.01–1% (at most 5%) per decade. To date, completely described fungi accounted for only 7% of the 1.5 million species hypothesis, i.e. a relatively conserved estimate. Average numbers of species newly described per year based on every decade evaluation was 1229 from 1980 to 1989, 1097 from 1990 to 1999 and 1196 from 1999 to 2009. A calculation shown that the average numbers of new species increased to 1430 each year from 2008 to 2012. However, it was assumed that the number of fungal species ranged between 3.5 and 5.1 million based on next-generation sequencing. In contrast, an updated estimate of fungal diversity showed that the fungal species ranged from 2.2 to 3.8 million worldwide. Here, a model was constructed to say the description rate of fungi through the Sigma State software (Sigma State 3.5. SPSS, USA). Numbers of known fungi from the series editions of "Dictionary of the Fungi" were taken into consideration; there was an exponential regression relationship between described fungal numbers and years ($R^2 = 0.99$, $p < 0.0001$). Based on this regression analysis, 1.5 million fungal species estimated by Hawksworth in 1991 could be described only by the year 2184. Similarly, the estimates of 2.2 and 3.8 million fungal species could be described by the years 2210 and 2245, respectively. Besides, it is important that data on biogeographic distributions, levels of endemism and host specificity must be considered when estimating the global fungal diversity. The above methods were hampered by the fact that all the data and estimates are based on ITS nr DNA sequence data, and it is now well known that this DNA locus is not well suited to reflect the true species diversity within a given genus or family. On the other hand, recent, intensive studies based on comprehensive inventories of certain fungal genera and families have proved that in countries and areas that were hitherto neglected by mycological taxonomists, up to over 90% of the collected specimens may constitute undescribed species. (4)

Fungi as Decomposers and Nutrient Recyclers

Role of Fungi in the Carbon Fungi play a crucial role in the balance of ecosystems. They colonize most habitats on earth, preferring dark, moist conditions. They can thrive in seemingly-hostile environments, such as the tundra. However, most members of the Kingdom Fungi grow on the forest floor where the dark and damp environment is rich in decaying debris from plants and animals. In these environments, fungi play a major role as decomposers and recyclers, making it possible for members of the other kingdoms to be supplied with nutrients and to live. The food web would be incomplete without organisms that decompose organic matter. Some elements, such as nitrogen and phosphorus, are required in large quantities by biological systems; yet, they are not abundant in the environment. The action of fungi releases these elements from decaying matter, making them available to other living organisms. Trace elements present in low amounts in many habitats are essential for growth but would remain tied up in rotting organic matter if fungi and bacteria did not return them to the environment via their metabolic activity. Cycle: Decomposition of Organic Matter. (5)

Symbiotic Relationships in Nature

In a parasitic relationship, the parasite benefits while the host is harmed. Parasitic fungi live in or on other organisms and get their nutrients from them. Fungi have special structures for penetrating a host. They also produce enzymes that break down the host's tissues. Parasitic fungi often cause illness and may eventually kill their host. They are the major cause of disease in agricultural plants.

Fungi have several mutualistic relationships with other organisms. In mutualism, both organisms receive help from the relationship. Two common mutualistic relationships involving fungi are mycorrhiza and lichen.

- A **mycorrhiza** is a mutualistic relationship between a fungus and a plant. The fungus grows in or on the plant roots. The fungus benefits from the easy access to food made by the plant. The plant benefits because the fungus puts out mycelia that help absorb water and nutrients. Scientists think that a symbiotic relationship such as this may have allowed plants to first colonize the land.
- A **lichen** is an organism that results from a mutualistic relationship between a fungus and a photosynthetic organism. The other organism is usually a cyanobacterium or green alga. The fungus grows around the bacterial or algal cells. The fungus benefits from the constant supply of food produced by the photo synthesizer. The photo synthesizer benefits from the water and nutrients absorbed by the fungus. Some fungi have mutualistic relationships with insects. For example:
- Leafcutter ants grow fungi on beds of leaves in their nests. The fungi get a protected place to live. The ants feed the fungi to their larvae.
- Ambrosia beetles bore holes in tree bark and "plant" fungal spores in the holes. The holes in the bark give the fungi an ideal place to grow. The beetles harvest fungi from their "garden." (6)

Fungi in Food Chains and Ecosystems

Ecology of Fungi

Fungi as Decomposers

Although decomposers, such as fungi, are generally located at the bottom of food chains, food webs, and energy pyramids, decomposers in the biosphere are vital for the health of the environment. By breaking down dead material, they provide the nutrients that other organisms need to survive. As decomposers feed on dead organisms, they release nutrients into the soil. Because they do not photosynthesize, fungi rely on organic sources of energy; they are heterotrophic. They are the primary decomposers (or saprotrophs) in many ecosystems. Most saprotrophic fungi grow as a branching network of hyphae. While bacteria can grow and feed only on the exposed surfaces of organic matter, fungi can use their hyphae to penetrate larger pieces of organic matter. Additionally, only fungi have evolved the enzymes necessary to break down plant carbohydrates like lignin and cellulose. Lignin is the tough complex carbohydrate found in wood, and cellulose is the complex carbohydrate found in plant cell walls. These two factors make fungi the primary decomposers in forests, where dead matter has high concentrations of lignin and is often in large pieces. Decomposers eventually convert all organic matter into carbon dioxide and nutrients. This releases raw nutrients (such as nitrogen, phosphorus, and magnesium) in a form usable to plants and algae. This process resupplies nutrients to the ecosystem, which allows for greater primary production. Fungi also use the nutrients for their own growth and repair.

Fungi as a Food Source

The fruiting bodies of fungi provide food for a wide variety of animals, from insects, slugs, and snails to rodents and larger mammals, such as deer and wild boars. Humans have collected and grown mushrooms for food for many thousands of years. However, many fungi have developed defence mechanisms that involve the production of toxins to discourage animals from eating them. (7)

Fungi and Human Health

Fungi in medicine

Fungi make important contributions in managing disease in humans and animals. Penicillin is based on fungi. Fungi are involved in the industrial processing of more than 10 of the 20 most profitable products used in human medicine. Drug discovery and research are ongoing. Uses of fungi in medicine include micafungin, an antifungal agent, mycophenolate, used to prevent tissue rejection, and rosuvastatin, which reduces cholesterol. Bread yeast is important in baking, but studies of bakers yeast also led to the discovery of basic cellular biochemistry and metabolism. In 1929 Alexander Fleming isolated substance from mold, and from there, penicillin was discovered. It was the first of a series of antibiotics derived directly from fungi that revolutionized the medical world from fungus was first used successfully to treat an infection caused by a bacteria in 1941. After this, many previously fatal diseases caused by bacteria became treatable. Several new groups of fungal agents have been discovered. The widely used antifungal agent Griseofulvin is derived from fungi. Griseofulvin is used to treat dermatophytes. It accumulates in the hair and skin following topical application. (8)

Fungal allergens

Airborne fungal spores occur widely and often in far greater concentrations than pollen grains. Immunoglobulin E-specific antigens (allergens) on airborne fungal spores induce type I hypersensitivity (allergic) respiratory reactions in sensitized atopic subjects, causing rhinitis and/or asthma. The prevalence of respiratory allergy to fungi is imprecisely known but is estimated at 20 to 30% of atopic (allergy-predisposed) individuals or up to 6% of the general population. Diagnosis and immunotherapy of allergy to fungi require well-characterized or standardized extracts that have the relevant allergen(s) of the proper fungus. Production of standardized extracts is difficult since fungal extracts are complex mixtures, and a variety of fungi are allergenic. Thus, the currently available extracts are largely nonstandard zed, even uncharacterized, crude extracts. Recent significant progress in isolating and characterizing relevant fungal allergens is summarized in the present review. Particularly, some allergens from the genera Alternaria, Aspergillus, and Cladosporium are now thoroughly characterized, and allergens from several other genera, including some basidiomycetes, have also been purified. The availability of these extracts will ease definitive studies of fungal allergy prevalence and immunotherapy efficacy as well as enhance both the diagnosis and therapy of fungal allergy. (9)

Fungal pathogens: diseases in humans, animal and plants

Fungi can affect animals, including humans, in several ways. A mycosis is a fungal disease that results from infection and direct damage. Fungi attack animals directly by colonizing and destroying tissues. Mycotoxicosis is the poisoning of humans (and other animals) by foods contaminated by fungal toxins (mycotoxins). Mycetoma describes the ingestion of preformed toxins in poisonous mushrooms. In addition, individuals who display hypersensitivity to Molds and spores develop strong and dangerous allergic reactions. Fungal infections are generally very difficult to treat because, unlike bacteria, fungi are eukaryotes. Antibiotics only target prokaryotic cells, while compounds that kill fungi also harm the eukaryotic animal host. Many fungal infections are superficial; that is, they occur on the animal's skin. Termed cutaneous ("skin") mycoses, they can have devastating effects. For example, the decline of the world's frog population in recent years may be caused by the fungus *Batrachochytrium dendrobatidis*, which infects the skin of frogs and presumably interferes with gaseous exchange. Similarly, more than a million bats in the United States have been killed by white-nose syndrome, which appears as a white ring around the mouth of the bat. It is caused by the cold-loving fungus *Geomyces destructans*, which disseminates its deadly spores in caves where bats hibernate. Mycologists are researching the transmission, mechanism, and control of *G. destructans* to stop its spread. (10) Fungi that cause the superficial mycoses of the epidermis, hair, and nails rarely spread to the underlying tissue. These fungi are often misnamed "dermatophytes", from the Greek words dermis meaning skin and phytic meaning plant, although they are not plants. Dermatophytes are also called "ringworms" because of the red ring they cause on skin. They secrete extracellular enzymes that break down keratin (a protein found in hair, skin, and nails), causing conditions such as athlete's foot and jock itch. These conditions are usually treated with over-the-counter topical creams and powders; they are easily cleared. More persistent superficial mycoses may require prescription oral medications. (11)

Fungi in Biotechnology and Industry

Fungi in food production

Fungi are also used for the production of fermented food and beverages in all traditional and indigenous cultures in the world. Examples include cheeses, bread, beer, wine, cider, rice, and soy sauce. Humans have exploited the natural abilities of fungi to ferment fruits and grains to produce alcoholic beverages and bread since as early as 6000 BCE (9–11) and for cheese since at least 7500 BCE. Yeasts are used for the fermentation of bread, wine, and beer, while filamentous fungi are used for the maturation of cheeses and soy sauce (from soybeans using *Aspergillus oryzae*) and the production of alcohol from rice (yielding sake, also using *A. oryzae*). In the south of France and other regions, a plant pathogenic fungus, *Botrytis cinerea*, is used to concentrate sugar in grape berries before collection, yielding "noble rot," which is a sweet and expensive wine. Some other filamentous fungi and yeasts are used to ferment and preserve meat from food spoilage, in particular *Penicillium nalgiovense*, which forms the white crust on salamis. (12) Cheese making by early Neolithic farmers was a major advance in food processing, allowing milk to be preserved in a nonperishable, transportable form and making it more digestible for adults, because cheese has much less lactose than fresh milk does. The earliest evidence of cheese making date from the 6th millennium BCE in Poland, with findings of the presence of milk fat in sieve vessels, and from the early Bronze Age (ca. 3,800 years ago), with the discovery of residues of old cheese in tombs. The earliest cheeses were simple, made by adding lactic acid bacteria (LAB) to fresh milk to provoke milk curdling and then draining in sieve vessels. The use of different mechanical processes to drain the curd, i.e., carving, brewing, pressing, grinding, heating, and the maturing of these cheeses, appeared later and gave rise to the large variety of cheeses known today (soft cheeses, blue-veined cheeses, hard cheeses, uncooked firm cheeses, and cooked firm cheeses). Microorganisms play a major role in the cheese-making process, from the initial milk curdling by LAB to the maturation step by fungi (including yeasts and Molds). Indeed, during ripening, microbiological and biochemical changes directly influence the development of the texture and flavour that make each kind of cheese unique. Primary biochemical changes include (i) lipolysis, in which LAB are the main actors by metabolizing lactose into lactate; (ii) proteolysis, which has a direct influence on flavour through the production of short peptides and amino acids, originating from six primary sources (e.g., the coagulant, the milk, starter LAB, nonstarter LAB), secondary starters (Molds such as *Penicillium roqueforti* in blue cheeses), and Gram-positive bacterial microflora on the surface of smear cheeses; and (iii) metabolism of residual lactose, lactate, and citrate. Secondary biochemical changes include metabolism of fatty acids and of amino acids by Molds such as *P. roqueforti* in blue cheeses and *Penicillium camembert* or *Geotrichum candidum* in soft cheeses such as Camembert and Brie. Microbial interactions within a cheese are thus crucial to produce a cheese with the desired texture and flavour, making the cheese substrate a complex but very interesting ecosystem in which to study microbial community interactions. (13)

Industrial application

Fungi are now widely used in industrial biotechnology, for example, as production hosts for technical and food and feed processing enzymes, as gene donors for such enzymes, as production hosts for organic acids and cholesterol-lowering drugs (the statins), and as starter cultures and probiotics. Around half of the industrial enzymes used globally are of fungal origin; the other half are of bacterial origin. However, this balance is now moving toward the use of more enzymes from a wider spectrum of families of the fungal kingdom. There are several reasons for this. Fungal enzymes are efficient, compatible, and suitable for industrial processing: they have sufficient protein stability to give the enzyme products an acceptable shelf life; they provide customer solutions, meet regulatory approval demands, and fulfil end user needs. The driver for this increased importance of fungi and fungal enzymes is the development of the new bioeconomy, where crop residues, industrial by-products, and organic waste streams are used as a basis for producing more bio-based products, obtaining more from biological resources, and wasting less. The potential is huge. Currently, there is a global loss of 30 to 50% of all agricultural production, when summing up losses through the value chain from field to end user. Because of this, it is predicted that fungal enzymes will be vital for moving from a fossil-based to a renewables-based world economy, where upgrade of lignocellulosic biomass leads to production of not only biofuels, but also bio-based materials and bio-based chemicals, as well as new and healthier feed and food ingredients. (14)

Fungi and Climate Change

The role of the environment in emerging and reemerging infectious diseases is increasingly recognized. Climate change, defined by the United Nations Framework Convention on Climate Change as “a change of climate which is attributed directly or indirectly to human activity that alters the composition of the global atmosphere and which is in addition to natural climate variability observed over comparable time periods” may create environmental pressures that result in new diseases caused by fungi.(15) While viral and bacterial diseases receive most attention as the potential cause of plagues and pandemics, fungi can arguably pose equal or even greater threats: There are no vaccines available yet for fungal pathogens, the arsenal of antifungal agents is extremely limited, and fungi can live saprotrophic Ally, producing large quantities of infectious spores and do not require host-to-host contact to establish infection. Indeed, fungi seem to be uniquely capable of causing complete host extinction. For the vast majority of fungal species, the capacity to grow at elevated temperatures limits their ability to infect and establish in mammals. However, fungi can be trained to evolve thermotolerance, and gradual adaptation to increasing temperature caused by climate change could lead to an increase of organisms that can cause disease. In addition, climate change can increase the geographic range of pathogenic species or their vectors, leading to the emergence of diseases in areas where they have not previously been reported. Environmental disruptions due to climate change such as floods, storms, and hurricanes can disperse and aerosolize fungi or implant them via traumatic wounds, resulting in infections by previously very rare or unknown fungal species. (16) It summarizes the potential effects of climate change, showing examples of emerging fungi and their consequences, along with the potential for new and currently unknown species to emerge. Climate change affects rainfall causing floods and drought and can increase tropical cyclone and tornado severity, leading to far-reaching human health impacts. The link between natural disasters and later fungal infections in disaster-affected persons is increasingly recognized, with an excellent review of this area by Benedict and Park. Disaster-associated fungi can be violently displaced and widely disseminated, leading to pulmonary and soft tissue infections by fungal species that may otherwise be uncommon. For example, a severe dust storm in the southern San Joaquin Valley of California in 1977 dispersed *Coccidioides amities* from Bakersfield, an area of high endemicity, to Sacramento County, where it is rare, resulting in more than 100 infections. (17)

CONCLUSION

Fungi have been used as a cell factory to produce enzymes and small molecule compounds for almost a century. The biomass produced during these production processes has generally been considered a waste stream. This inconvenience may change in the future since fungal biomass is now being explored as the basis of sustainable biomaterials. In agriculture, the presented applications have the potential to improve crop yield, reduce the use of synthetic fertilizers and pesticides, avoid the use of toxic compounds, and promote sustainable agriculture practices. (18) Therefore, further attention must be paid to uncovering the biomolecules from fungi for agriculture and pharmaceutical applications through studying metagenomics, genomics, and proteomics. (19)

Humans are endowed by evolution with robust defences against invasive fungal diseases, successfully treating many of them. However, we are still vulnerable to invasive fungal infections. People suffering from opportunistic and primary invasive fungal infections urgently need resources and research efforts to bring them new diagnostics and treatments regardless of commercial potential. Enormous work over the past three decades has opened vast new views in fungal biology; we can expand upon them to fulfil the promises of modern medical advances. (20)

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