

The good, the bad and the tasty: The many roles of mushrooms

K.M.J. de Mattos-Shipley^{1,2}, K.L. Ford¹, F. Alberti^{1,3}, A.M. Banks^{1,4}, A.M. Bailey¹, and G.D. Foster^{1*}

¹School of Biological Sciences, Life Sciences Building, University of Bristol, 24 Tyndall Avenue, Bristol, BS8 1TQ, UK; ²School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK; ³School of Life Sciences and Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, UK; ⁴School of Biology, Devonshire Building, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK

*Correspondence: G.D. Foster, Gary.Foster@bristol.ac.uk

Abstract: Fungi are often inconspicuous in nature and this means it is all too easy to overlook their importance. Often referred to as the “Forgotten Kingdom”, fungi are key components of life on this planet. The phylum *Basidiomycota*, considered to contain the most complex and evolutionarily advanced members of this Kingdom, includes some of the most iconic fungal species such as the gilled mushrooms, puffballs and bracket fungi. Basidiomycetes inhabit a wide range of ecological niches, carrying out vital ecosystem roles, particularly in carbon cycling and as symbiotic partners with a range of other organisms. Specifically in the context of human use, the basidiomycetes are a highly valuable food source and are increasingly medicinally important. In this review, seven main categories, or ‘roles’, for basidiomycetes have been suggested by the authors: as model species, edible species, toxic species, medicinal basidiomycetes, symbionts, decomposers and pathogens, and two species have been chosen as representatives of each category. Although this is in no way an exhaustive discussion of the importance of basidiomycetes, this review aims to give a broad overview of the importance of these organisms, exploring the various ways they can be exploited to the benefit of human society.

Key words: Agaricomycete, Basidiomycete, Model species, Mushroom.

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INTRODUCTION

The basidiomycetes are a large and incredibly diverse phylum of fungi, which, together with the ascomycetes, make up the sub-kingdom *Dikarya* – often referred to as the “higher fungi”. Basidiomycetes are almost exclusively filamentous fungi that have complex lifecycles, reproduce sexually and produce basidiospores on specialised cells called basidia. This review has chosen to focus specifically on the class *Agaricomycetes*, which make up 98 % of the *Agaricomycotina* – the largest subphylum of the basidiomycetes. Taxonomically, *Agaricomycetes* is roughly analogous to the previously accepted *Homobasidiomycetes*, a name which is no longer used due to the recognition that not all members of this phylogenetic group have homobasidia (undivided basidia). *Agaricomycetes* includes the most conspicuous basidiomycete species, all of which produce basidiocarps, such as the gilled mushrooms, bracket fungi, puffballs, crust fungi, chanterelles, coral fungi and jelly fungi (Hibbett 2006).

The morphology of agaricomycete fungi is incredibly varied. The cyphelloid fungi, for example, produce small cup or tube-shaped basidiocarps which rarely exceed 2 mm in length and diameter (Bodensteiner *et al.* 2004). At the other end of the spectrum are species such as *Phellinus ellipsoideus*, which is responsible for producing the largest fruiting body ever recorded, weighing between 400 and 500 kg (Dai & Cui 2011). *Agaricomycetes* can also claim to contain some of the largest and oldest organisms on earth. In 1992, a genetically stable individual *Armillaria gallica* was shown to cover 15 hectares, weigh upwards of 10 000 kg and was aged at 1 500 yr old (Smith *et al.* 1992). In 2000, an individual colony of *Armillaria ostoyae* was identified in Oregon which was said to cover an incredible 965

hectares and estimated to be between 1 900 and 8 650 yr old (Ferguson *et al.* 2003).

In addition to being morphologically varied, agaricomycetes fill a wide range of ecological niches. A very large number of species are wood-decay fungi, which play a vital role in carbon cycling. Other species function as symbiotic partners, including symbionts of insects (Aanen *et al.* 2002, Mueller *et al.* 2005), but most notably as mycorrhizal plant-symbionts, which are essential for the survival of many plant species (Kohler *et al.* 2015). There are also parasitic and pathogenic agaricomycete species, with pathogens of timber and crop species being of particular importance (Brazee & Wick 2009, Farid *et al.* 2009). Human pathogenic fungi are generally limited to the ascomycetes, although *Schizophyllum commune* has been known to cause serious lung infections (Chowdhary *et al.* 2013). Although less common, agaricomycete species are increasingly being discovered in a variety of freshwater (Frank *et al.* 2010), marine (Hibbett & Binder 2001, Binder *et al.* 2006, Amend *et al.* 2012) and mangrove environments (Baltazar *et al.* 2009). Recently a new aquatic species of gilled mushroom belonging to the genus *Psathyrella* has been identified, which produces completely submerged fruiting bodies (Frank *et al.* 2010).

The ecological roles of agaricomycetes make them important within human societies due to the roles they play in industries such as forestry and agriculture, but they also impact us more directly, as a valuable source of nutrients and as medicinally relevant species. The vast majority of edible fungi are agaricomycetes, with the exception of the truffles and morels, which are ascomycete species. The most toxic fungi are also agaricomycetes however, such as the death cap, *Amanita phalloides*, which is responsible for the majority of fatal mushroom poisonings (Litten 1975).

Despite the relatively conspicuous nature of agaricomycete species and their relevance to human societies, they have not always garnered as much attention within the scientific community as other fungi, largely due to the relative difficulty in growing and studying them within laboratory settings. However, with the advent of modern molecular techniques, such as transformation systems and next generation sequencing, this fascinating and indispensable group of organisms are now becoming more and more accessible, and therefore the ways in which they can be exploited for human endeavours is increasing greatly.

This review will attempt to give an overarching perspective of the importance of the *Agaricomycetes*, by focusing upon selected species which we feel are representative of the main roles these fungi play within natural ecosystems and in the context of serving a particular purpose to human societies: as model species, as edible species, as decomposers, as toxic species, as medicinal mushrooms, as symbionts and as pathogens.

MODEL AGARICOMYCETES

The in-depth study of model species within all Kingdoms serves to deepen our understanding of the key biological processes shared by all life-forms, including evolution, genetics, cell biology, meiosis and pathogenesis. Fungi play a unique role in understanding such broad biological themes, sitting as they do between plants and animals in the tree of life, and in fact being more closely related to animals than plants, with the Fungi and Animalia Kingdoms being part of a monophyletic clade (Baldauf & Palmer 1993).

Being well understood and genetically tractable, model species not only inform our general understanding of life, but also serve as the foundation for extended research into the biology of other related species. As previously mentioned, one factor that has hampered the study of basidiomycetes has been the relative difficulty in studying these organisms in laboratory conditions. Therefore, detailed and systematic investigations into model species, and the subsequent development of molecular tools specifically adapted for basidiomycetes, have been vital in making the phylum as a whole more accessible.

This review will consider two model agaricomycetes: *Coprinopsis cinerea* and *Schizophyllum commune*. Both species have been studied in great detail, with thousands of peer-reviewed papers published elucidating key aspects of basidiomycete biology and describing the development of tools and techniques applicable to such species. This resulting body of knowledge has formed the basis of much of our understanding of this fascinating phylum.

Coprinopsis cinerea

Coprinopsis cinerea (Fig. 1A), commonly known as the “gray shag”, is a model multicellular basidiomycete (Redhead *et al.* 2001), which has been studied extensively. In nature, *C. cinerea* is found globally where it employs a saprotrophic lifestyle, favouring habitats containing dung and compost (Kjalke *et al.* 1992, Kues 2000). *Coprinopsis cinerea* is a coprinoid mushroom, collectively known as the “inky caps”, due to the fact that their caps liquefy on maturation to aid the dispersal of

basidiospores. As deliquescence occurs from the bottom of the gills upwards, the edges of the cap curl to expose mature spores to wind currents for dispersal (Pukkila 2011). The coprinoid basidiomycetes are an excellent example of convergent evolution, as recent molecular analyses have demonstrated that although they share this common trait, they are not in fact all closely related in evolutionary terms (Redhead *et al.* 2001).

Much of *C. cinerea*'s value as a model species lies in the fact that it is easy to cultivate on petri dishes in the laboratory, where mating and the full life cycle can be completed in just two weeks. A suite of molecular tools have now been developed for *C. cinerea*, including an established transformation system (Binninger *et al.* 1987, Granado *et al.* 1997, Collins *et al.* 2010, Dörnte & Kües 2012), a selection of marker genes (Kilaru *et al.* 2009b), gene silencing methods (Namekawa *et al.* 2005, Wälti *et al.* 2006, Heneghan *et al.* 2007, Costa *et al.* 2008) and strains which have been engineered to allow targeted gene disruption, a technique which is generally not feasible for agaricomycetes (Nakazawa *et al.* 2011). The genome sequence for *C. cinerea* also became available in 2010, revealing a haploid genome size of 37.5 Mbp (Stajich *et al.* 2010). This relative ease of working with *C. cinerea* and the available tools means extensive research has been carried out on many fundamental aspects of the biology of this species.

For example, the sexual reproduction of *C. cinerea* has been studied in great detail. As is now known to be typical for basidiomycetes, *C. cinerea* has two distinct stages to its lifecycle: as a primary monokaryote (from the Greek, mono = one; karyos = kernel or nucleus), which contains only one haploid nucleus per cell, and as a fertile dikaryote which contains two nuclei per cell (Fig. 1B). Dikaryotic mycelium forms when two sexually compatible monokaryotic hyphae fuse in a process called plasmogamy (Kues 2000, Raudaskoski & Kothe 2010). Unlike in the lifecycle of many plants and animals, karyogamy (nuclear fusion to produce a diploid cell) does not occur immediately for basidiomycetes and instead the dikaryotic state, with two distinct haploid nuclei per cell, is stably maintained indefinitely. Dikaryotic tissues can generally be recognised due to their vigorous growth and the presence of clamp connections at the hyphal septa, which are specialised structures that elegantly maintain the presence of two distinct nuclei in each cell (Fig. 1C).

When the necessary genetic and environmental factors coincide, fruiting bodies will then form from the dikaryotic mycelia, differentiating into three main tissue types: gill, stalk and cap. This differentiation process is incredibly complex and occurs via a well-defined developmental process that requires light/dark cycles and takes approximately one week (Fig. 1D). It is on the external surfaces of the gills in the basidia that nuclear fusion then occurs, followed by meiosis, and finally, haploid basidiospore formation (Kues 2000). After release and dispersal, these basidiospores germinate to produce a monokaryotic mycelium, thus completing the sexual lifecycle. Like 90 % of basidiomycetes, *C. cinerea* is heterothallic, meaning that two different and compatible monokaryons are required for mating to produce fertile dikaryons that are capable of fruiting and producing sexual spores. The remaining 10 % of basidiomycetes are homothallic, meaning that their spores germinate to produce fertile mycelia capable of fruiting (Raper 1966). *Agaricus bisporus*, one of the species discussed later in this review, is an interesting example of a basidiomycete where different varieties employ different lifestyles, including homothallic and heterothallic.

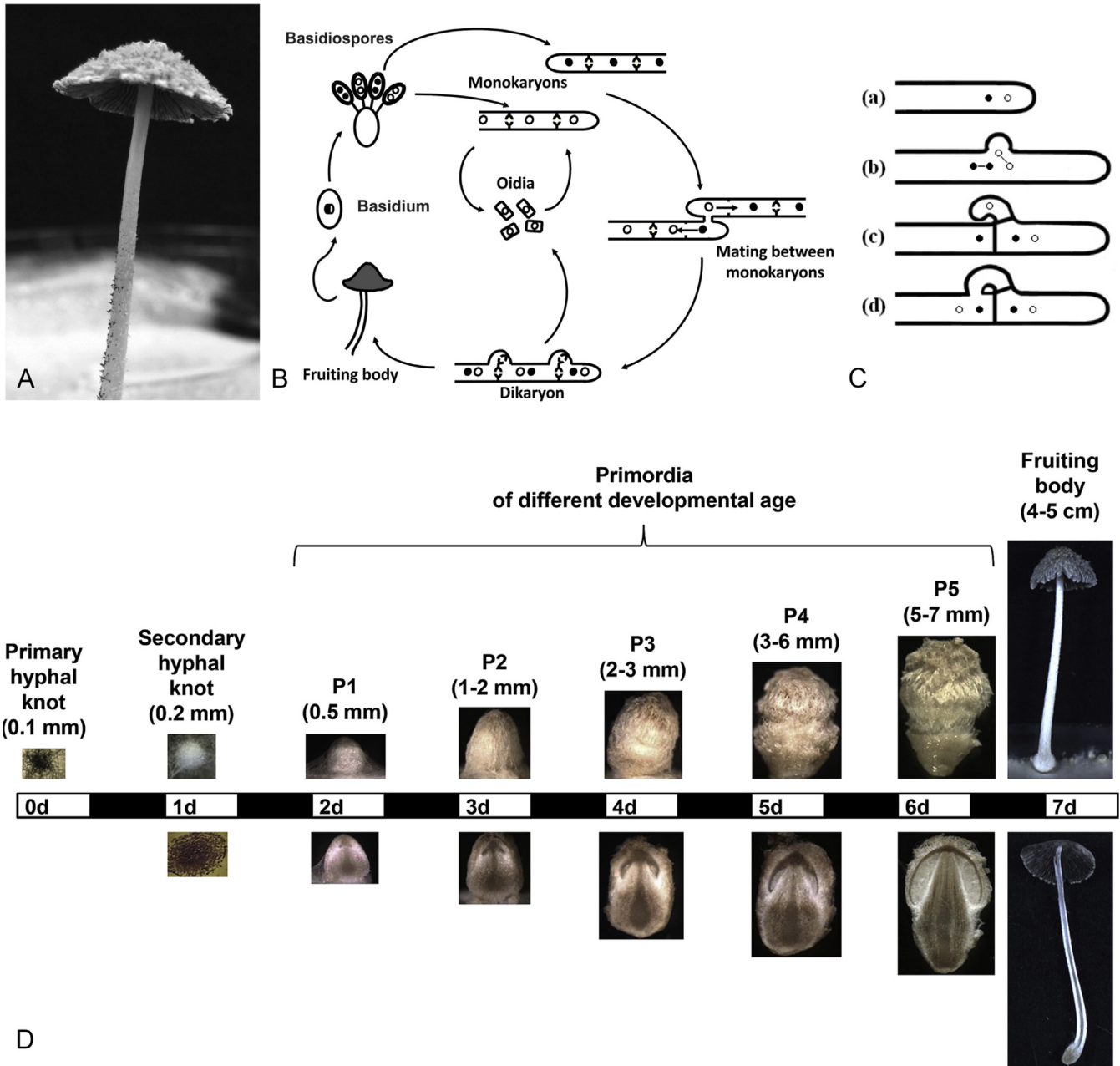


Fig. 1. **A.** Under laboratory conditions mature *Coprinopsis cinerea* fruiting bodies form from dikaryotic mycelia, allowing mushroom development to be studied. Reproduced from [Stajich et al. \(2010\)](#) © National Academy of Sciences. **B.** The lifecycle of *Coprinopsis cinerea*, reprinted from [Raudaskoski \(2015\)](#) with permission from Elsevier. **C.** Clamp connections are a unique feature of dikaryotic basidiomycetes, and are likely to be involved in maintaining the presence of both nuclei types in each cell during mitosis. **D.** Fruiting body development of *C. cinerea* strain AmutBmut. The central bar represents the light and dark phases (12 h each) over a seven day period. Structures were harvested at the beginning of each light phase – outer views and longitudinal sections are shown. Fruiting development for *C. cinerea* is hemiangiocarpic, in that the developing fruiting body is initially enclosed (angiocarpic), opening before full maturity (gymnocarpic). Reprinted from [Kües & Navarro-González \(2015\)](#) with permission from Elsevier.

Investigations into the lifecycle of *C. cinerea* have been instrumental in uncovering the genetic regulation of sexual compatibility in basidiomycete fungi. In *C. cinerea*, compatibility is controlled at two genetic loci: the A (*MAT-A*) and B (*MAT-B*) mating type loci ([Raudaskoski & Kothe 2010](#), [Plaza et al. 2014](#)). The *MAT-A* locus of *C. cinerea* (now also known as the HD locus) contains genes encoding two classes of homeodomain transcription factors. These need to heterodimerize to become an active transcription factor, which in turn activates the A-regulated developmental pathway, controlling nuclear division and the formation of clamp connections in the dikaryotic tissue ([Kües 2015](#)). This active dimer can only form in non-self combinations, meaning that the nuclei from the two original monokaryotic strains must have different alleles at this locus to be compatible.

The *MAT-B* locus of *C. cinerea* (now also known as the PR locus) encodes small pheromone peptides and G protein-coupled receptors. A successful interaction between pheromones and receptors can also only take place if they are from different B loci (non-self), and the binding of these pheromones to the receptors induces a signal transduction pathway that regulates nuclear migration and the fusion of clamp connections with the adjacent cell. This need for compatibility at two separate loci is known as a tetrapolar system because the progeny of a dikaryon each display one of four mating types (e.g. AB, Ab, aB and ab). The need to differ at both loci means that a fertile cross between sibling progeny can only occur 25 % of the time, but the existence of a high number of different alleles at both loci in the general population means that the chances of being compatible

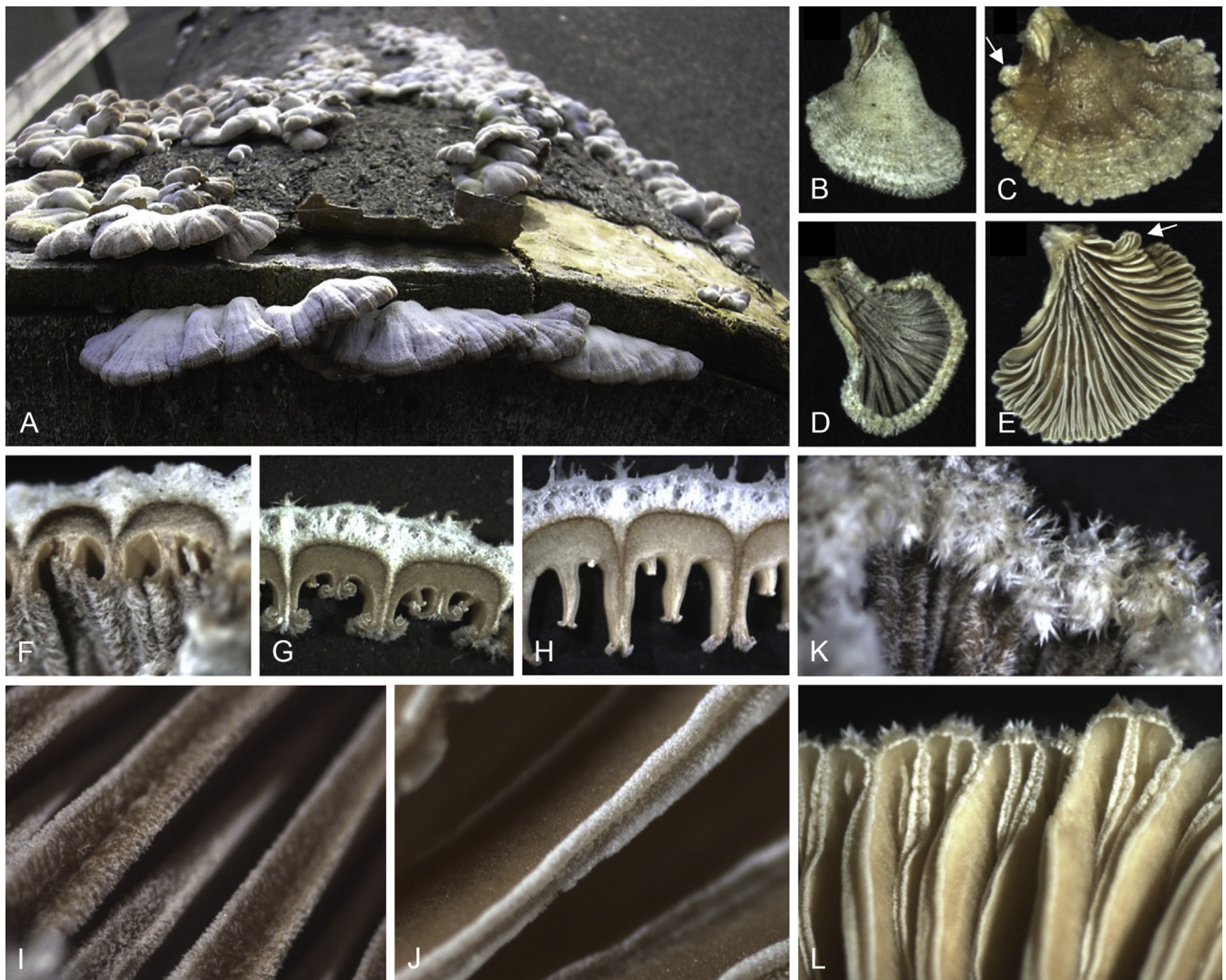


Fig. 2. *Schizophyllum commune*, the split gill fungus. **A.** Mature *S. commune* fruiting bodies growing on a felled beech trunk. **B–E.** Dorsal (**B** and **C**) and ventral (**D** and **E**) views of a wild-collected *S. commune* fruiting body, under dry conditions where the fruiting body is enrolled (**B** and **D**), and moist conditions where the fruiting body is unfolded (**C** and **E**). **F–H.** Cross sections through a mature fruiting body, demonstrating the morphological differences under dry (**F** and **G**) and moist conditions (**H**). **I–J.** Show the outer edges of the lamellae in dry and moist conditions respectively. It is the ‘splitting’ of the pseudolamellae (gills) under dry conditions, as seen in **I**, which earns this species its common name. **K–L.** Show the outer edges of the fruiting body under dry and moist conditions respectively. Under dry conditions, the outer edge with abhymenial hairs is enrolled over the youngest hymenia (fertile surfaces). Under moist conditions, the hymenia are exposed. Reprinted from [Kües & Navarro-González \(2015\)](#) with permission from Elsevier.

with a non-related individual is very high. The total population of *C. cinerea* has been estimated to contain 164 A alleles and 79 B alleles ([Day 1963](#)), meaning that there are over 12 000 different mating types.

In addition to being a model species, *C. cinerea* has been shown to produce a wide profile of enzymes and secondary metabolites including lectins, laccases, peroxidases, and terpenoids ([Bouws et al. 2008](#), [You et al. 2014](#)). One major group of secreted compounds produced by *C. cinerea* are the laccases, which play a role in the degradation of lignin in plant fibres, vital for *C. cinerea*'s role as a decomposer ([Kilaru et al. 2006a, b](#), [Courty et al. 2009](#)) and of potential use in various industries such as fibre board production and waste treatments. A novel antimicrobial peptide, copsin, has also been discovered from this species, which was previously thought not to produce any antimicrobial compounds ([Essig et al. 2014](#)). This recent discovery suggests that despite the thorough analysis of this model organism to date, there is likely to be a wealth of capabilities yet to be discovered.

Schizophyllum commune

Schizophyllum commune, or the “split-gill” mushroom ([Fig. 2](#)), is a generalist, saprotrophic species that is found worldwide and has been utilised as a model system for studying basidiomycete mating and mushroom development since the early 20th century ([Kniep 1920](#), [Essig 1922](#), [Linder 1933](#), [Whitehouse 1949](#), [Raper & Miles 1958](#)). *Schizophyllum commune* is classed as a white rot fungus (see ‘[Decomposing basidiomycetes](#)’ section), which has been responsible for extensive post-harvest losses of hay and silage and has been reported as an occasional pathogen of woody species ([Brady et al. 2005](#)). *Schizophyllum commune* is also an emerging pathogen of mammals and humans, with reports of bone and soft tissue infection in dogs ([Kano et al. 2002](#), [Tanaka et al. 2008](#)), and sinusitis and infections of soft tissue, lung and nails in humans, although largely in immunocompromised patients ([Chowdhary et al. 2013](#), [Tsukatani et al. 2015](#)). Most recently, *S. commune* has been isolated from an infected harbour seal ([Hanafusa et al. 2016](#)).

This incredibly flexible lifestyle means that *S. commune* can be found in a very wide range of habitats, and is considered to be the most wide-spread and abundant basidiomycete, with the single species existing on every continent except Antarctica (Watling *et al.* 1991). One unusual trait, which helps facilitate such wide geographic distribution, is its adaptations to climatic variability. The fruiting bodies of *S. commune* can dehydrate and rehydrate many times over the course of a growing season, maintaining the ability to sporulate and removing the need to produce costly fruiting bodies multiple times. These fruiting bodies can also function as exceptional longer-term survival structures: basidiocarps desiccated and vacuum-stored for 35 yr have been shown to retain the ability to sporulate following rehydration (Essig 1922, Bisby 1945).

Like *C. cinerea*, *S. commune* arose as an ideal agaricomycete for study due to its ease of manipulation in the laboratory: it fruits readily *in vitro* and can complete its lifecycle within 10 d (Kües & Navarro-González 2015). Also like *C. cinerea*, it was used in pioneering research into basidiomycete sexual reproduction; elucidating the tetrapolar system and uncovering the genetic basis of compatibility control (Giasson *et al.* 1989, Stankis *et al.* 1992, Specht 1995, Kothe 1999). *Schizophyllum commune* has a very similar tetrapolar system to that of *C. cinerea*, with two unlinked genetic complexes, one encoding homeodomain transcription factors and the other encoding pheromones and receptors. However, it is worth noting that there are differences between the two species, both in the number of gene at each locus and the genetic organisation (Raudaskoski 2015). In the case of *S. commune*, there are estimated to be 288 different alleles at the *MAT-A* locus and 81 alleles at the *MAT-B* locus (Raper 1966), meaning that this species is estimated to have over 23 000 different mating types – an incredibly efficient way of maintaining out-breeding whilst optimising the chances of being compatible with any non-related isolates. The simultaneous uncovering of the tetrapolar mating systems of *C. cinerea* and *S. commune* has since facilitated the discovery of similar mating loci in various species, including *Laccaria bicolor* (Niculita-Hirzel *et al.* 2008), *Flammulina velutipes* (van Peer *et al.* 2011), *Lentinula edodes* (Wu *et al.* 2013b) and *Pleurotus eryngii* (Kim *et al.* 2014).

Although both model species discussed here employ a tetrapolar heterothallic lifestyle, it must be noted that 30–40 % of basidiomycetes are bipolar, with compatibility being controlled by only one locus (Kues 2000). This can occur when the two mating loci become genetically linked, effectively acting like a single locus (Lee *et al.* 1999, Lengeler *et al.* 2002), but there are also examples where one locus has lost its self/non-self discrimination (James *et al.* 2006, James *et al.* 2011).

Schizophyllum commune was utilised in many early studies of fruiting, demonstrating that environmental conditions including light, temperature, CO₂ and nutrient availability regulate fruiting (Essig 1922, Niederpruem & Wessels 1969, Perkins & Gordon 1969). In dikaryotic *S. commune*, light induces asymmetrical growth at colony margins which initiates the formation of the hyphal knots that develop into primordia and then mature into the split-gill basidiocarps bearing the haploid basidiospores (Kües & Navarro-González 2015).

Moving into the modern molecular era, *S. commune* has continued to be at the forefront of agaricomycete molecular genetic research. It was the first basidiomycete for which a

transformation system was established (Munoz-Rivas *et al.* 1986) and some of the initial regulatory sequences used for heterologous gene expression in agaricomycetes were obtained from *S. commune* (Harmsen *et al.* 1992). It was also the first agaricomycete in which GFP, now a ubiquitous molecular tool, was expressed. This highlighted the importance of introns for efficient expression in many basidiomycetes, a requirement not seen in other fungal phyla such as the Ascomycetes (Lugones *et al.* 1999, Scholtmeijer *et al.* 2001). Such discoveries concerning the fundamental nature of basidiomycete genetics have paved the way for similar work in other agaricomycete species (Ma *et al.* 2001, Burns *et al.* 2005, Kilaru *et al.* 2009a).

Correspondingly, numerous molecular tools are now available for *S. commune*. The genome was sequenced in 2010 (Ohm *et al.* 2010b), there are several selectable markers, both auxotrophic and antibiotic (Munoz-Rivas *et al.* 1986, Schuren & Wessels 1994, Scholtmeijer *et al.* 2001), a range of strong and inducible promoters (Munoz-Rivas *et al.* 1986, Harmsen *et al.* 1992) and various tools for functional gene analysis, including RNAi-mediated gene silencing (de Jong *et al.* 2006) and unusually for agaricomycete fungi, an efficient method of gene knockout by homologous recombination (de Jong *et al.* 2010, Ohm *et al.* 2010a). The availability of these tools has facilitated analysis of gene function in *S. commune*, for example identifying genes that are essential in mushroom development (Ohm *et al.* 2011) and identifying homologues of the blue light receptors in *Neurospora crassa*, which are important for light recognition in *S. commune* (Ohm *et al.* 2013).

Schizophyllum commune has also been vital in the discovery and understanding of hydrophobins, and was the first species from which a hydrophobin was isolated (Wessels *et al.* 1991). Hydrophobins are a very important class of proteins produced exclusively by fungi that are capable of spontaneously self-assembling at hydrophilic–hydrophobic interfaces, creating amphipathic monolayers. This layer is typically found on the surface of aerial hyphae and spores. In the former, it is thought to reduce the surface tension of the medium in which the fungus is growing, allowing the hyphae to breach the air–water interface, and also stops water logging from occurring (Lo *et al.* 2014). By making the surface of spores hydrophobic, the hydrophobin layer is thought to be essential for dispersal. Hydrophobins are also thought to play a protective role during fruiting body formation (De Groot *et al.* 1996), and there is evidence for various roles in pathogenic fungi, including masking the immunogenicity of airborne fungal spores, effectively by acting as an invisibility cloak (Aimanianda *et al.* 2009). The various unique properties of hydrophobins mean they have potential applications in many industries, including nanotechnologies such as coating implanted medical devices, as biosensors and as cell growth surfaces (Lo *et al.* 2014). One hydrophobin from *S. commune*, SC3, demonstrates immunomodulatory activity (Akanbi *et al.* 2013) and thus has potential as a therapeutic agent in cancer treatment.

As a prolific producer of plant cell wall degrading enzymes including cellulases, hemicellulases and pectinases, *S. commune* also has potential use in bioremediation (Irrshad & Asgher 2011, Saini *et al.* 2013) – a research area discussed in more depth in the “Decomposing basidiomycetes” section of this review.

EDIBLE BASIDIOMYCETES

Perhaps the most obvious value of basidiomycetes to human cultures is as a food source. Mushrooms are an excellent source of nutrients, being low in calories and fats and free of cholesterol whilst providing proteins, vitamins, fibre and minerals such as potassium, iron and phosphorus. The consumption of mushrooms goes back to ancient times, with Ancient Romans referring to them as a “divine food”, believing that they were the result of lightning thrown down by Jupiter. The Egyptians believed that they were a gift from the god Osiris (Manzi et al. 1999).

There are considered to be thousands of species of edible mushrooms worldwide and the foraging of such mushrooms is conducted globally. Many species, such as the Chanterelle, are considered delicacies. However, only 25 or so species have been cultivated and only 10 commercialised. The consumption of mushrooms increased steadily during the second half of the 20th century as commercial production became widespread, with consumption recorded as 495 127 tonnes in 1961, increasing to 4 210 714 tonnes in 2000 (FAOSTAT). An even more dramatic increase has been seen so far in the 21st century, with the latest FAO statistic from 2013 being 9 926 966 tonnes.

As basidiomycetes are cultivated using lignocellulosic substrates and other organic waste matter, this industry can be considered as the only known industry that simultaneously addresses two of the major challenges faced by today’s growing population: providing food with high nutritional value whilst reducing waste and environmental pollution.

In this section, we will discuss the two most cultivated species worldwide, *Agaricus bisporus* and *Pleurotus ostreatus*.

Agaricus bisporus

Agaricus bisporus is probably the most famous of the edible mushrooms. It is known by various common names, depending on its colour and maturity, including the button mushroom, chestnut mushroom, portobello mushroom and champignon mushroom. *Agaricus bisporus* is a litter-decomposing saprotroph which is found globally in habitats such as forests and grasslands (Kerrigan 1995, Hildén et al. 2013). The wild varieties typically have a pale grey-brown cap, which is 5–10 cm in diameter when mature (Fig. 3A). It is the most widely cultivated species in the world, produced on the scale of millions of tons every year, with a global market of several billion US dollars (Kerrigan 2013).

Agaricus bisporus owes its Latin name to the unusual spore production of *A. bisporus* var. *bisporus*, the most abundant variety in wild populations and the variety from which all of the traditional cultivars are derived. In most basidiomycetes, four spores form on each basidium (tetrasporic), each containing one of the four products of meiosis. Each spore then germinates into monokaryotic mycelia, which needs to mate with another compatible monokaryotic strain to produce the fertile dikaryotic mycelium. *Agaricus bisporus* var. *bisporus* has predominantly bisporic basidia (Fig. 3B), meaning that it produces two spores per basidium. Each of the two spores contain two non-sister post-meiotic nuclei, resulting in the germination of a fertile dikaryotic strain (Kerrigan et al. 1993). This life-cycle is known as secondary homothallism, or pseudohomothallism. A second variety of the button mushroom, called *A. bisporus* var. *burnettii*, was discovered in California in the early 1990s, and was shown instead to have a predominantly heterothallic life cycle, with tetrasporic

basidia being formed in approximately 90 % of the cases (Kerrigan et al. 1994). Each spore contains one type of nucleus and thus germinates to produce non-fertile monokaryotic mycelia, which need to mate to complete the lifecycle. As *A. bisporus* is a bipolar species, with mating compatibility being controlled by one locus, the offspring of an individual will be compatible with one another 50 % of the time. Lastly, a rare third variety was discovered by Callac et al. (2003), and named *A. bisporus* var. *eurotetrasporus*. The specimens ascribed to this variety, collected in France and Greece, have tetrasporic basidia like *A. bisporus* var. *burnettii* but with much longer spores, and this variety employs a predominantly homothallic life cycle (Kamzolkina et al. 2006), meaning that monokaryotic mycelia which germinate from an individual spore are capable of fruiting. See Fig. 3C for a schematic representation of the life cycles of the three varieties.

Cultivation of *A. bisporus* has been refined over the years, but is believed to have begun around 1650 in France (Chang & Hayes 1978). Commercial farming takes place in mushroom houses under controlled conditions of temperature, humidity and aeration. A few crucial steps can be identified in this process (Hudson 1986, Carlile et al. 2001), such as preparation of the substrate, or “compost”, which is typically made of horse manure and wheat straw. Several pathogens and competitors can hamper cultivation, so pasteurisation of the substrate is carried out prior to inoculation. Inoculum of pure culture (also known as “spawn”) is prepared by growing the fungus on a sterile substrate made of wheat or rye. This spawn is mixed with the pasteurised compost and incubated at 25 °C to allow for mycelial growth. Fruiting is then induced by performing the “casing” which involves covering the mycelium with peat and chalk and placing the trays at 16–18 °C. Overall harvesting of mushrooms usually occurs 9–11 wk after inoculation (Fig. 3D).

The intensive cultivation and study of *A. bisporus* has served to highlight the types of microbes that infect mushrooms. There are several ascomycete fungi that parasitise the fruiting bodies or vegetative mycelia of basidiomycetes, such as *Lecanicillium fungicola*, the causative agent of “dry bubble” (Ameijer et al. 2003, Bailey et al. 2013b) and *Mycogone perniciosa*, the causative agent of ‘wet bubble’ (Gea et al. 2010). Symptoms of infection include masses of undifferentiated mycelia rather than fruiting bodies, or developmental aberrations and distortions such as comb-like protrusions of gill tissue on the upper surfaces of the cap (called rosecomb), as seen in *M. perniciosa* infections (Umar & Van Griensven 1999). Bacterial pathogens, including a number of *Pseudomonas* species, cause necrotic lesions on fruiting bodies (Abou-Zeid 2012). Various mycoviruses cause disease in *A. bisporus*, such as brown cap mushroom disease (Eastwood et al. 2015) and La France disease (Borodynko et al. 2010), which impact both the yield and quality. And finally, insect pests have a significant impact of the commercial cultivation of *A. bisporus*, with the two major classes of pests being the sciarids and phorids (Jess & Bingham 2004).

In addition to being a well-known culinary species, *A. bisporus* is also known for its ecological role as a lignocellulose decomposer (Wood & Leatham 1983). This was investigated at the molecular level by Morin et al. (2012), who sequenced the genome of the fungus and carried out transcriptomic analyses to compare gene expression at different developmental stages and culturing conditions. They found that when the fungus is grown on compost, there is considerable upregulation of genes involved in the degradation of lignocellulose, including those encoding carbohydrate-active enzymes (CAZy) and oxidoreductases, as well as protein degradation and peptide transporters. Rather than

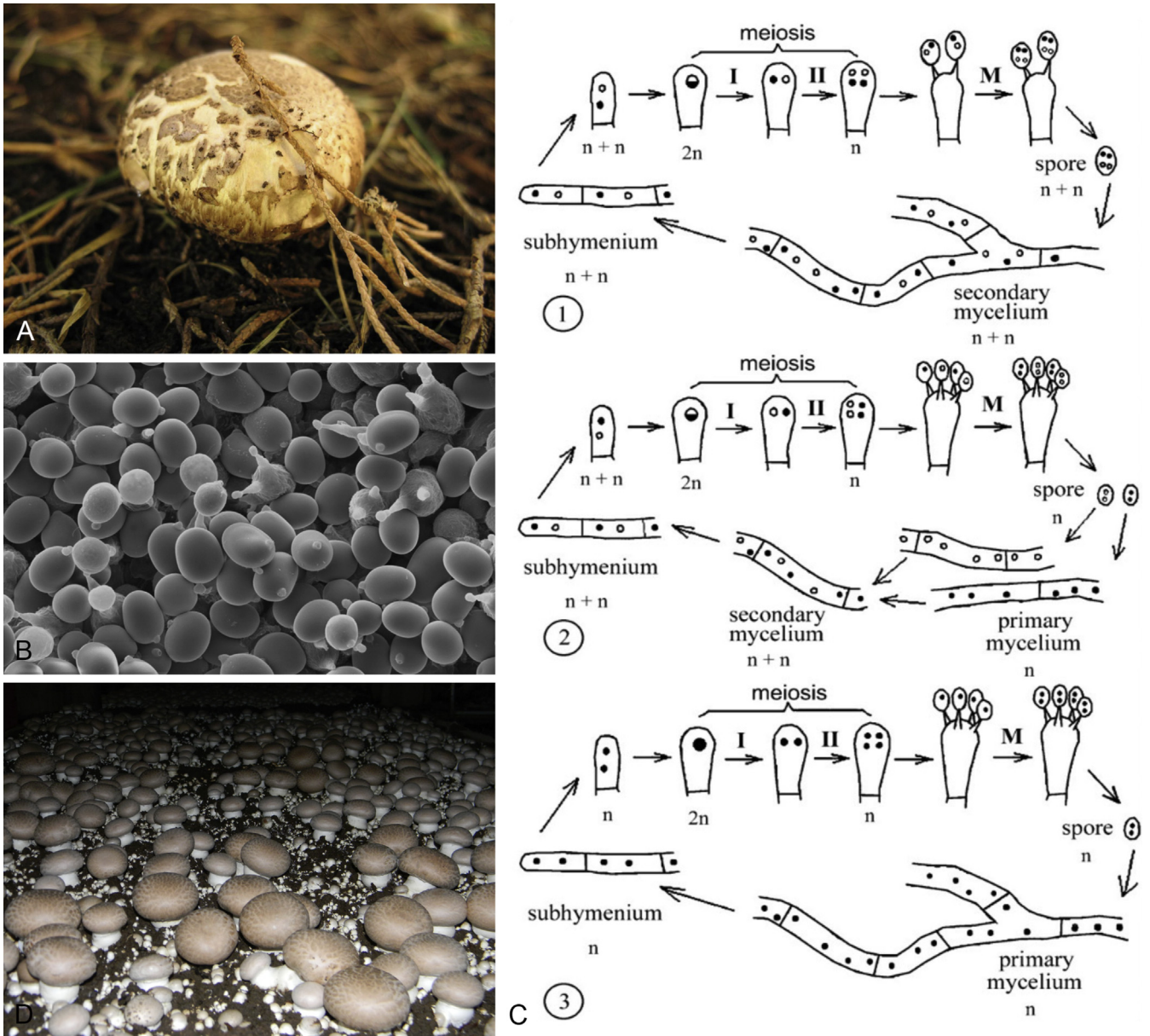


Fig. 3. **A.** *Agaricus bisporus*, commonly known as the button mushroom, growing in the wild (Copyright © Nathan Wilson). **B.** An electron micrograph of *A. bisporus* var. *bisporus* showing the release of spores from bisporic basidia, courtesy of Louisa Howard, Dartmouth College. **C.** A representation of the three life cycles of *Agaricus bisporus*. 1: In *A. bisporus* var. *bisporus* pseudohomothallism is predominant, where multinucleate spores germinate to produce dikaryotic mycelia. 2: In *A. bisporus* var. *burnettii* heterothallism is prevalent. Spores from tetrasporic basidia, containing only one nucleus each, germinate to produce non-fertile homokaryotic mycelia that needs to mate to complete the lifecycle. 3: In *A. bisporus* var. *eurotetrasporus* homothallism is predominant. Homokaryotic spores germinate to produce mycelia which, although homokaryotic, is fertile and capable of fruiting (Kamzolnikina *et al.* 2006). This image is reprinted with permission from Mycologia. (Copyright © The Mycological Society of America). **D.** *A. bisporus* being cultivated in mushroom beds (Copyright © Tim Sage).

being attributed to either of the two most popular classes of wood degrading fungi (white rots and brown rots), *A. bisporus* is considered to be a humicolous species that has found its ecological niche in humic-rich environment, where partially decomposed organic matter prevails (Morin *et al.* 2012). A protease called serine proteinase 1 (SPR1) is expressed by *A. bisporus* in response to environmental cues such as nitrogen availability (Heneghan *et al.* 2009), and has recently been shown to play a key role in nutrient acquisition for *A. bisporus*, allowing colonisation of compost (Heneghan *et al.* 2016).

Pleurotus ostreatus

Pleurotus ostreatus is the second most cultivated mushroom after *Agaricus bisporus* (Rühl *et al.* 2008). *Pleurotus ostreatus*

was first scientifically named *Agaricus ostreatus* in 1774, later being moved to the newly recognised genus *Pleurotus* in 1871 by the German mycologist Paul Kummer (Naraian *et al.* 2016). As with many fungal species, the name is descriptive. The Latin *Pleurotus* (sideways) refers to the sideways growth of the stem with respect to the cap seen in fungi of this genus. *Ostreatus* (Latin: oyster) refers to the shape of the cap, which resembles, and is considered by some to taste similar to, the bivalve oyster (Fig. 4). This is also the origin of the common name for this species: the “oyster mushroom”, although it is additionally known as the tree oyster mushroom or grey oyster mushroom to differentiate it from other *Pleurotus* species. In Japan it is known as Hiratake, which means “flat mushroom”. As well as the offset position of the stipe and fan-shaped cap, *P. ostreatus* can be recognised by various morphological features. The cap ranges in



Fig. 4. **A.** The basidiocarps of *Pleurotus ostreatus* growing on the trunk of a fallen Red Oak (*Quercus Rubra*) tree in Washington State Park, New Jersey. (Copyright © I. G. Safonov). **B.** On a Coast Live Oak (*Quercus agrifolia*) in Oakland, California. (Copyright © Alan Rockefeller). **C.** And in a cultivated setting, where a polyethylene bag filled with a suitable lignocellulosic substrate has been inoculated with spawn (Copyright © Alan Rockefeller). **D.** A paralysed nematode worm being penetrated by *P. ostreatus* hyphae, which obtain valuable nitrogen from the worm (image courtesy of Prof. George Barron, University of Guelph). **E.** *Pleurotus ostreatus* spores (Copyright © Alan Rockefeller).

diameter from 5–25 cm, is smooth and is usually white to light brown but can also be grey or even dark brown, with the flesh being white. The gills are decurrent and the spore print is white to lilac grey (Glaeser & Smith 2010).

Pleurotus ostreatus is a saprotrophic species, being a primary decomposer of wood, and of beech trees in particular. It is typically found growing out from trees in shelf-like clusters. This species is sometimes confused with *Lentinellus ursinus*, a species that occupies the same niche, is widely distributed in North America and has a strong acid taste.

In nature, *P. ostreatus* is found throughout the North Temperate Zone, including most of Asia where it is particularly popular as a culinary mushroom, Britain and Ireland, and most

of mainland Europe. It is also present in North America, with the exception of the Pacific Northwest where other closely related species can be found. Taxonomically, *P. ostreatus* is part of a complex of very closely related and morphologically similar species, such as *P. pulmonarius* and *P. populinus* (also known as oyster mushrooms) and as such distribution data can be unclear.

Unlike *A. bisporus*, the history of *P. ostreatus* cultivation is very recent. The first attempts to grow *P. ostreatus* as a food source were during the Second World War in Germany as a subsistence measure. A study on the breeding potential of *P. ostreatus*, published in 1976, described *P. ostreatus* as a “New Cultivated Mushroom”, proposing its potential as a “future crop”

(Eger *et al.* 1976). Since that time, the cultivation of *P. ostreatus* has rapidly become a worldwide phenomenon. Although a variety of cultivation techniques are employed, the general process of cultivation is the same as for other edible mushrooms, with a pure culture (spawn) being used to inoculate a suitable substrate. In the case of *P. ostreatus*, a very wide range of lignocellulosic substrates can be used, including – but not limited to – coffee pulp, sawdust, weed plants, cotton from the textile industry, molasses from the sugar industry, peanut and coconut shells and cassava peels. A mixture of cottonseed hulls and wheat straw, which has a high water holding capacity, is a commonly used substrate. The substrate is generally milled, pasteurised, spawned and then used to fill polyethylene bags (Fig. 4C). Various free-standing or suspended systems are then used, which produce mushrooms for harvesting 3–4 wk after spawning.

Many different factors affect the productivity of cultivation, including the strain, the substrate, the type of spawn, the moisture level and various physicochemical conditions, and much work has been done investigating such variables for *Pleurotus ostreatus* (Sánchez 2010). In terms of the strain used, natural variation can be utilised, but strain improvement, particularly genetic manipulation, is increasingly applied to develop desirable characteristics. Long-term exposure to *P. ostreatus* spores has been known to trigger various respiratory allergies and as such, one aspect of strain improvement is focusing on the development of sporeless mutants (Sharma & Sharma 2014).

Beyond its role as a culinary basidiomycete, being a white rot fungus *P. ostreatus* plays an important role in decomposition and carbon cycling and has garnered significant attention for its potential use as a bioremediation agent (Eggen & Majcherczyk 1998, Hirano *et al.* 2000, Byss *et al.* 2008, Miele *et al.* 2010, Purnomo *et al.* 2010). Genome sequencing has recently revealed the wood-degrading machinery of *P. ostreatus* to be typical of white rot fungi (Riley *et al.* 2014). *Pleurotus ostreatus* has also been shown to produce β -glucans, which have marked anticarcinogenic and cardioprotective properties, and as such could fall into the medicinal category. Finally, *P. ostreatus* is one of the basidiomycete species known to be capable of carnivory, killing and digesting nematodes as a nitrogen source (Fig. 4D) (Thorn & Barron 1984, Thorn *et al.* 2000). There has been some interest in such carnivorous basidiomycetes as biocontrol agents to circumvent the environmental concerns over the use of conventional nematicides (Morton *et al.* 2004, Balaes & Tanase 2016).

DECOMPOSING BASIDIOMYCETES

One of the most vital ecological roles played by fungi is that of the recyclers. By decomposing substrates such as lignocellulose in wood, which cannot be degraded by any other organisms, they release vital nutrients back into the environment. As such, it can be said that all life relies on the presence of fungi to recycle the basic building blocks needed for growth and survival. Different types of basidiomycetes have evolved to degrade specific types of organic compounds and wood decaying species and genera are traditionally divided into two main categories; brown rot and white rot. Brown rot fungi primarily decompose the white-coloured cellulose present in wood via a Fenton reaction-based mechanism, leaving the brown-coloured lignin largely

intact. White rot fungi in comparison, are unique in their ability to completely degrade the brown-coloured lignin, before enzymatically degrading the cellulose layer (Riley *et al.* 2014). This initial degradation of the brown-coloured lignin polymers gives the decomposing wood a bleached appearance, hence the name 'white rot'.

This section will discuss two species which are representative of the two wood-degrading categories: the brown rot fungus *Serpula lacrymans*, and the model white rot fungus *Phanerochaete chrysosporium*. *S. lacrymans* is the causative agent of the dry rot of timber, causing hundreds of millions of pounds worth of damage each year globally (Palfreyman 2001). *P. chrysosporium* on the other hand is a species with the potential to be highly beneficial to human societies, by harnessing its metabolic capabilities for use in a wide range of industries.

Serpula lacrymans

Brown rot fungi are exclusively basidiomycete species and account for 6 % of wood-decomposing fungi (Gilbertson 1980). The most destructive brown rot species is considered to be *Serpula lacrymans* (Fig. 5), a crust fungus which causes a condition known as dry rot, due to the ability of this species to grow on surfaces containing very little or no apparent moisture (Jennings & Bravery 1991).

The history of dry rot by *S. lacrymans* dates back several centuries, with the first reliable reports coming from wooden vessels in the 17th century (Ramsbottom 1937, Ramsbottom 1953). Regarding its general biology, this species is found in nature exclusively on conifers, including species of the genera *Pinus* and *Abies*, tending to colonise large trunks with a diameter of more than 1 m at the base (Kausserud *et al.* 2012), and its temperature range spans between 3 and 26 °C, with an optimum of 21 °C (Jennings & Bravery 1991). *Serpula lacrymans* is believed to have a typical basidiomycete life cycle, with a predominant dikaryotic stage and dispersal of monokaryotic basidiospores. Flat brown fruiting bodies form primarily at the base of the trunk of the host plant, and have incredibly varying dimensions, from a few centimetres to more than one metre (Kausserud *et al.* 2012).

Phylogenetic studies have been conducted with the aim of understanding the evolutionary history of *S. lacrymans*. High genetic variation seen for specimens collected in north-east Asia suggests that this species may have originated in this region (Kausserud *et al.* 2007), and it is believed that *S. lacrymans* originally existed on mountains in temperate regions, typically at altitudes of more than 2 000 m. (Kausserud *et al.* 2012). From this primary environment, *S. lacrymans* is believed to have spread to the other presently colonised areas, which include Japan, Oceania, Europe and North and South America. Phylogenetic studies also indicate that current isolates of *S. lacrymans* could be ascribed to two different lineages: var. *shastensis* (found growing on conifer forests) and var. *lacrymans* (the cause of dry rot of timber) (Kausserud *et al.* 2007).

This species has become publically notorious for its extraordinary ability to grow on and decompose wooden building elements, particularly softwoods, and it has been estimated that the damage caused in the US is comparable to that of termites (Alexopoulos *et al.* 1996). It is commonly claimed that fungi cannot grow on wood that has a water content of less than 20 %, which is more than normally found in buildings. However,

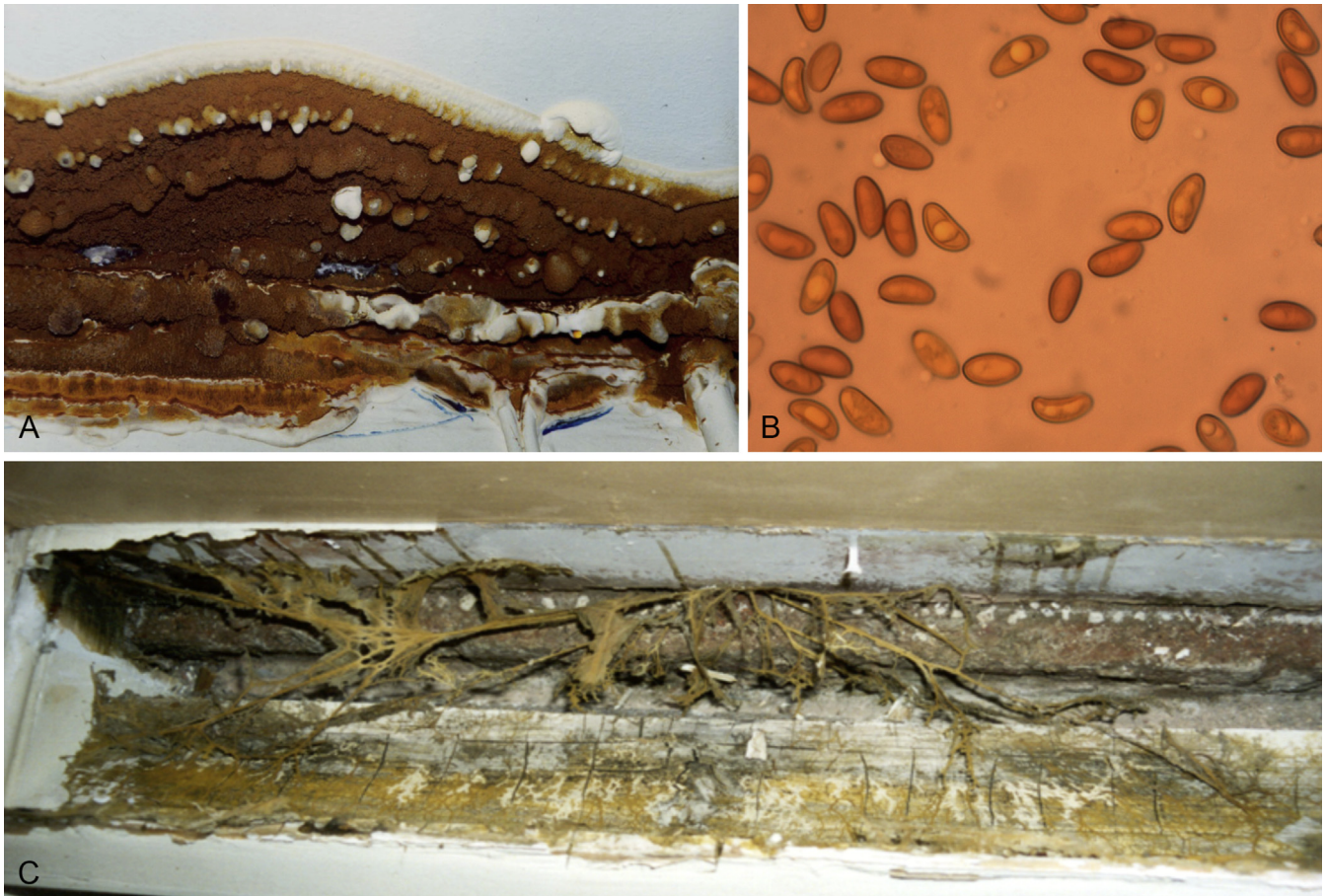


Fig. 5. **A.** The fruiting body of *Serpula lacrymans*, the causative agent of dry rot of timber (Copyright © Malcolm Storey/www.discoverlife.org). **B.** *S. lacrymans* spores are released from the fruiting body for air dispersal (photograph taken by Andrzej Majcherczyk from the University of Göttingen, courtesy of Ursula Kües). **C.** When nutrients become scarce, *S. lacrymans* produces rhizomorphs. Also known as mycelial cords, rhizomorphs can travel considerable distances, even penetrating brickwork, plaster and masonry to reach another food source.

conditions such as the proximity of dripping pipes and general dampness can increase the water content of timber sufficiently to promote proliferation of *S. lacrymans*.

A feature that enables *S. lacrymans* to colonise dead wood and survive in spatially intermittent conditions of moisture and nutrients is the ability to produce rhizomorphs, like the honey fungus *Armillaria mellea* discussed later in this review. In *S. lacrymans* the rhizomorphs, which are linear aggregates of somatic hyphae, arise from a colonised wooden structure when residual nutrients are scarce (Kausarud *et al.* 2012). This organ-like cluster of hyphae grows five times faster than normal hyphae, and can extend a considerable distance away from the substrate, thus enabling the fungus to reach another host to colonise through the formation of a new mycelium (Fig. 5C). A unique system of vessels inside the hyphae of the rhizomorph allows for translocation of water and nutrients (Isaac 1991). These structures can also grow through plaster, brickwork and masonry, allowing the fungus to spread through buildings (Singh 1994).

Decomposition of wood by *S. lacrymans*, as with other brown rot fungi, is initiated by the biological disruption of wood polymers by hydroxyl radicals. The hydroxyl radicals are produced extracellularly via a Fenton reaction, mediated by reductants such as 2,5-dimethoxy-1,4-benzoquinone (2,5-DMBQ), which are produced by the fungus (Shimokawa *et al.* 2004, Korripally *et al.* 2013). The small size of the reductants needed to drive this reaction means that they can penetrate the intact cell wall, without the need for initial enzymatic degradation of lignin. Once

the lignocellulose matrix has been disrupted by the hydroxy radicals, cellulose-degrading enzymes can then gain access. This non-enzymatic way of achieving initial degradation of the lignocellulose differs from the enzymatic approach seen in the ancestral white rot fungi (see next section). The recent sequencing of the *S. lacrymans* genome, together with a comparative genomic and transcriptomic analysis assessing the evolution of the brown rot lifestyle, demonstrated that brown rot species have indeed lost the enzymatic apparatus of ligninolysis (Eastwood *et al.* 2011).

Serpula lacrymans represents a clear example of how evolution can act both at the metabolic level – through generation of a particular degradation apparatus – and at the morphological level – via the production of specialised organ-like structures – to enable the fungus to grow in unfavourable conditions and establish its own ecological niche, making it become the most aggressive rot fungus known to the construction industry.

Phanerochaete chrysosporium

Phanerochaete chrysosporium is another resupinate, or “crust” fungus, meaning that rather than producing the fruiting bodies known as mushrooms or toadstools, which are typical of agaricomycete fungi, the fruiting body lies flat on the substrate with the hymenium at the periphery or over the whole surface of the colony, appearing as no more than a crust. It is adapted to moderate to high temperatures and as such has a fairly wide

geographical distribution, covering North America, Europe and extending across to Iran.

In terms of lifestyle, *P. chrysosporium* is the model white rot fungus. White rot fungi are the only species capable of lignin degradation and it is this initial selective degradation of the brown-coloured lignin in the wood, leaving primarily the white-coloured crystalline cellulose, which gives them their name (Fig. 6A). The ability to degrade lignin lies, at least partly, in the ability to produce extracellular lignocellulolytic enzymes, the main examples being lignin peroxidase and manganese peroxidase. Lignin peroxidase, first isolated from *P. chrysosporium* in 1983 (Tien & Kirk 1983), degrades lignin via an oxidative process, the mechanism of which is thought to involve free radical pathways, utilising hydrogen peroxide as an oxygen source. Manganese peroxidase was isolated from *P. chrysosporium* in 1985 by two research groups simultaneously (Glenn & Gold 1985, Paszcyński *et al.* 1985). This enzyme preferentially oxidises manganese(II) ions and the resulting Mn(III) ions then oxidise the phenolic compounds in lignin directly, thus attacking the numerous and varied bonds in the lignin complex (Hofrichter 2002). In nature, *P. chrysosporium* therefore plays an essential ecological role recycling recalcitrant lignocellulose plant debris, especially when you consider that lignin is the most abundant aromatic carbon in the biosphere (Hofrichter 2002). Scarce nutrients such as nitrogen, phosphorus and sulphur, which are embedded in lignin tissues, are also released and made available. The degradation products of lignin can then be internalised by *P. chrysosporium*, where diverse intracellular enzymes such as cytochrome P450-dependant oxidases further metabolise them. An incredible repertoire of P450s (more than 150) has been identified within the genome of *P. chrysosporium* (Doddapaneni *et al.* 2005). The free radical based mechanisms of lignases, giving them broad specificity, combined with the incredible enzymatic capabilities of *P. chrysosporium* combine to make this species capable of degrading a very wide range of compounds, including aromatic, alicyclic, and aliphatic compounds.

It is these metabolic capabilities of *P. chrysosporium*, which gives this species huge potential in various applications. Firstly, within the biofuel industry, where lignocellulosic biomasses from either agricultural or forestry wastes are abundant, but to be used in biofuel production they require hydrolysis into simple sugars. Harnessing the lignin-degrading repertoire of enzymes produced by white rot fungi such as *P. chrysosporium* is one approach being used to release the cellulosic material from its lignin component (Chaturvedi & Verma 2013).

The high specificity with which *P. chrysosporium* degrades lignin, leaving cellulose largely intact, combined with its fast growth rate and thermostability, means it could also be employed by the paper pulping industry as a method of biobleaching. The dark colour of pulp and paper mill effluent makes it a significant environmental pollutant. By limiting photosynthesis and increasing water temperature, the effluent leads to a decrease in dissolved oxygen concentrations in aquatic ecosystems (Kringstad & Lindstroem 1984), and traditional bleaching agents are also environmental pollutants, making biobleaching an attractive alternative.

Phanerochaete chrysosporium could also be used to recycle or degrade materials previously thought to be entirely non-biodegradable. For example, in 2006, *P. chrysosporium* became the first organism known to be capable of degrading phenolic resins (PRs) (Gusse *et al.* 2006), which have structural similarities with lignin (Fig. 6B–C). PRs are complex synthetic polymers made from phenol and formaldehyde, which are

thermoset and are incredibly stable and resistant to degradation. It is this durability that makes them so popular, particularly in the construction industry, but it also makes them extremely difficult to degrade or recycle, so most PR products become permanent fixtures in landfills after their initial use. Although methods for recycling the synthetic polymer have been developed, they typically involve intensive heat and the use of solvents, which introduce additional waste management problems and make them too costly to be adopted on a large scale. With the global PR consumption recorded as 3 200 000 metric tons in 2004, and demand still growing (Pilato 2010), it is important that a method is developed to recycle and reuse these materials.

In addition to recycling PRs, another application of this species to the phenolic residue industry is to detoxify the phenol containing effluents. Such phenolic industrial effluents are severely toxic to aquatic life, and are harmful to human health, even in low concentrations, so represent a severe environmental pollutant, which requires addressing. A recent publication has demonstrated the applicability of specialised *P. chrysosporium* pellets made up of cells called chlamyospore-like cells (CLCs) for treating industrial wastewater containing phenolic compounds (Hailei *et al.* 2016). In CLC cells the ligninolytic enzymes are not excreted and as such they act as naturally immobilised enzymes, providing a low cost biomaterial for phenol wastewater treatment. This would also apply to phenol containing effluents from refineries, petrochemical, iron and steel industries.

The degradation of phenolic compounds is just one example of the bioremediation potential of white rot fungi such as *P. chrysosporium*. Other toxic compounds degraded by *P. chrysosporium* include DDT, TNT, PCBs and PAHs. PAHs are of particular concern due to their carcinogenic and mutagenic effects, such as the highly carcinogenic benzo(a)pyrene found in coal tar, which has been shown to be metabolised by *P. chrysosporium* (Bhattacharya *et al.* 2012). One potential application of such fungal degradation capabilities would be to decontaminate soil in industrial sites to allow safe redevelopment.

The final application of *P. chrysosporium* that will be mentioned here is as a biosorption agent. Biosorption (the binding and concentration) of heavy metals has been demonstrated by various fungal species. *P. chrysosporium* has been shown to be efficient at absorbing cadmium(II), lead(II) and copper(II), so there is great potential to use this species to safely remove metals from wastewater and contaminated environments (Yetis *et al.* 1998). A technique has recently been developed to use modified *P. chrysosporium* to remove the highly toxic chromium(VI) (Chen *et al.* 2011).

TOXIC BASIDIOMYCETES

The production of mycotoxins by basidiomycetes, and the resulting risk associated with ingesting certain species, is well known. Most mushroom poisoning, also known as mycetism or mycetismus, occurs following misidentification of a toxic species as an edible one and this accounts for hundreds of deaths globally each year (Graeme 2014). There are also, however, reports of poisonous mushrooms being used in assassinations. One such story is that of the Roman Emperor Claudius, said to have been deliberately poisoned by his wife Agrippina who laced a meal of Caesar's mushrooms (*Amanita caesarea*) with the death cap mushroom (*Amanita phalloides*) (Wasson 1972).

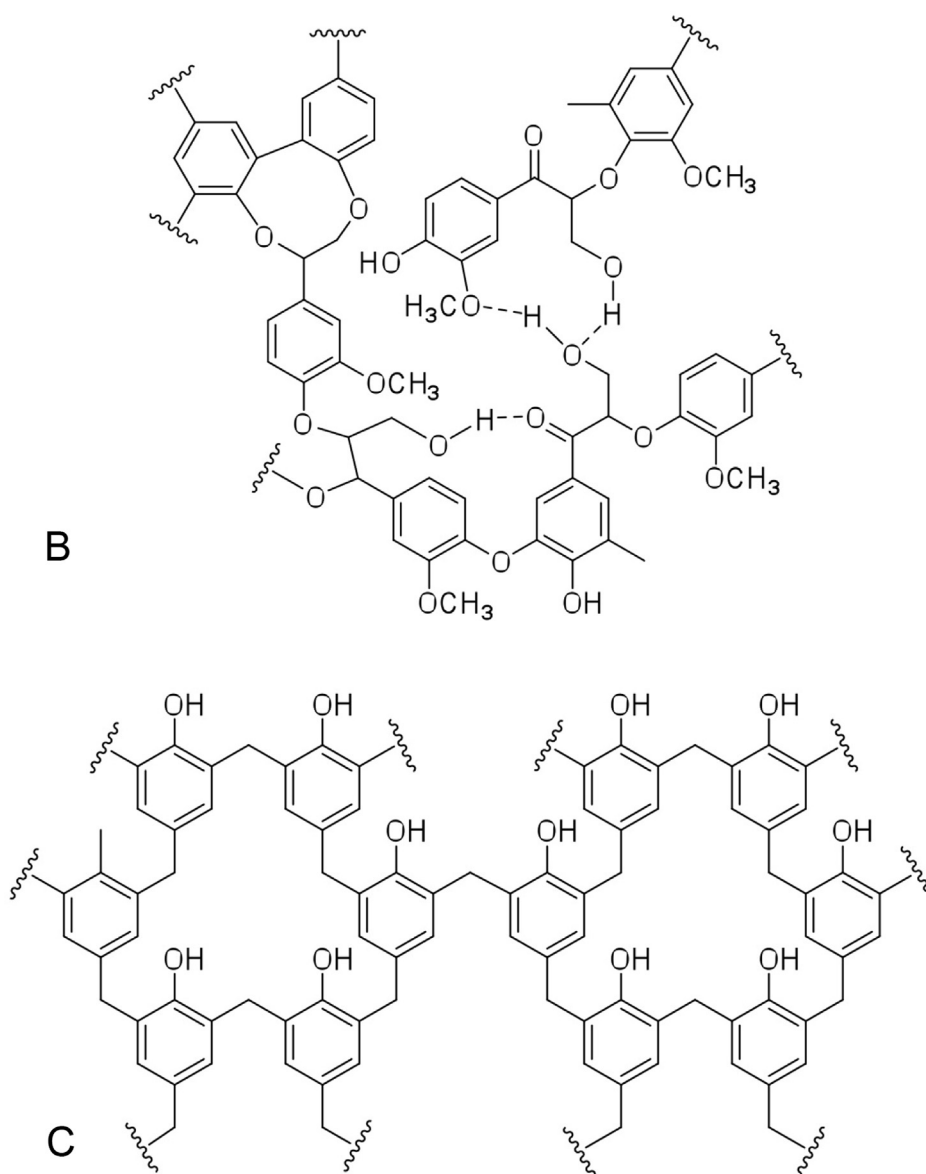


Fig. 6. A. *Phanerocheate chrysosporium*, a white rot fungus, so-called due to the bleached appearance of wood degraded by such species. **B–C.** Show the structures typical of lignin and phenol-formaldehyde resins respectively. The structural similarities mean that the natural metabolic capabilities of fungi such as *P. chrysosporium* can be used to degrade – and therefore recycle – persistent man-made materials such the phenol-formaldehyde resins.

Certain mycotoxin producing basidiomycetes are also intentionally ingested due to their psychedelic effects (Tyls *et al.* 2014).

In this section we will discuss *Psilocybe semilanceata*, the best known of the ‘magic mushrooms’, and *Amanita muscaria*, the quintessential toadstool and type species of the *Amanita* genus. Although reports of fatalities from *A. muscaria* poisoning are extremely rare, it is closely related to some of the most poisonous species known, including the destroying angels (*A. virosa* and *A. bisporigera*) and the death cap (*A. phalloides*) (Allen *et al.* 2012).

Psilocybe semilanceata

Psilocybe semilanceata is one of the best-known of the psychedelic mushrooms. This species is commonly known as the liberty cap due to its resemblance to the Phrygian cap; a cap which originated in the ancient country of Phrygia in Asia Minor but became a symbol of liberty during the French revolution, gaining the name of the ‘liberty cap’. The *Psilocybe* genus is distributed worldwide, existing in most biomes, with the greatest species diversity being found in the neotropic ecozone, and particularly Mexico (Guzmán *et al.* 1998, Ramírez-Cruz *et al.* 2013). The genus is now restricted to the hallucinogenic species with *P. semilanceata* as the conserved type species (Redhead *et al.* 2007, Ramírez-Cruz *et al.* 2013). This species is most commonly found in the cool temperate regions of the northern hemisphere with maritime influence, particularly bicoastal Northern America and Europe (Guzmán 1983, Redhead 1989). It has been recorded in some warmer or more southern climates, such as India (Barthakur *et al.* 2000) and Chile (Guzmán 2009), but in these regions related species are more prevalent and the reports are now suspect.

The preferred habitats of *P. semilanceata* are grassy meadows and fields, particularly north facing fields that have been fertilised by the faeces of ruminants such as sheep and cattle. Unlike the related psychedelic species *P. cubensis*, *P. semilanceata* does not grow directly on dung but is saprobic and feeds off decaying grass roots nearby (Keay & Brown 1990). It typically has fruiting bodies with a small cap (5–25 mm diameter and approximately twice as tall), which are hygrophanous, meaning the colour and appearance depends on the state of hydration. When dry it is pale in colour, a light yellow brown, but when wet it ranges from light to dark chestnut brown and has radial striations that correspond to the gills underneath (Fig. 7A). The gills are only very slightly attached to the stalk (adnexed), and are pale when young, becoming a darker purple-black as the spores mature (Musshoff *et al.* 2000).

Plants and fungi have been exploited for their psychotropic effects since prehistoric times (Guzmán 2009), and although some such ritualistic traditions – particularly by the Aztecs – are well documented, there is a relatively sparse record for *P. semilanceata* use. The first reliable record of *P. semilanceata* intoxication, which was accidental rather than intentional, was published in 1799 (Brande 1799). A British family had collected mushrooms from Green Park in London to use in a meal. The family's father and four children were reported to experience symptoms now known to be typical of psilocybin ingestion, including spontaneous laughter, delirium and pupil dilation. Evidence for the ritual use of a *Psilocybe* species in prehistoric Europe has recently been uncovered for the first time, in the form of post-Paleolithic rock art in Spain, which is thought to be

6 000 yr old (Akers *et al.* 2011). However, this is thought to depict the use of *Psilocybe hispanica*, a closely related mushroom endemic to a neighbouring region of Spain. The oldest suspected depiction of psilocybin use (approx. 7 000–9 000 yr old) is a painted mural from southeast Algeria, portraying mushrooms that have tentatively been identified as *P. mairei* (Akers *et al.* 2011).

The psychotropic effects of *Psilocybe* mushrooms are due to the presence of the compounds psilocybin and psilocin. These compounds were first isolated, identified and named by the chemist Albert Hoffmann in 1959, from samples of *P. mexicana* sent to him by the French mycologist Roger Heim (Hofmann *et al.* 1959). Psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine) is a prodrug which is quickly hydrolysed in the body to give psilocin (4-hydroxy-*N,N*-dimethyltryptamine), the pharmacologically active compound (Fig. 7B). This compound acts on serotonin receptors in the brain by acting as a partial agonist at the serotonergic receptors 5-HT_{1A} and 5-HT_{2A} (Passie *et al.* 2002). The commonly reported physical effects include pupil dilation, changes in heart rate, nausea, tremors, changes in blood pressure and dysmetria. The psychological effects are highly variable and influenced by the mindset and environment of the user, but can include giddiness, euphoria and joy but also depression, anxiety and paranoia. Hallucinations and distortions in the perception of time are also common, so although the mind-altering effects of psilocin typically last from two to six hours, it is reported that time can seem significantly longer for the user.

Although most cases of ingesting the liberty cap occur without incident or hospitalisation, and death from psilocybin alone has never been recorded, some isolated cases have had severe consequences. In 1998, an 18-yr-old man suffered from Wolff–Parkinson–White syndrome, arrhythmia and a myocardial infarction. In 2009, a teenager was reported to suffer cardiac abnormalities usually seen in Tako-Tsubo cardiomyopathy (Nef *et al.* 2009). In addition to the direct effects of *P. semilanceata* ingestion, there have been cases of novice collectors confusing *P. semilanceata* for a toxic basidiomycete called *Cortinarius rubellus*. In at least one case this resulted in end-stage renal failure, requiring a kidney transplant (Franz *et al.* 1996).

As well as being produced by *P. semilanceata*, psilocybin is produced by upwards of 200 fungal species. The majority (over 150 species) belong to the *Psilocybe* genus, with multiple other species belonging to the genera *Gymnopilus*, *Panaeolus* and *Copelandia*, amongst others (Guzmán 2005, 2009). Possession of any psilocybin containing ‘magic mushroom’, including *P. semilanceata*, is now illegal in most countries, although for a time after its discovery, pure psilocybin was marketed and sold to physicians and clinicians by Sandox (now Novartis), for use in psychedelic psychotherapy (Livingstone 2015). Recently there has been a resurgence in interest in the potential medicinal benefits of psilocybin, particularly as a treatment for OCD (Wilcox 2014), and cluster headaches (Sewell *et al.* 2006).

Amanita muscaria

Amanita is one of the best-known fungal genera, containing some of the most poisonous species of basidiomycetes known. Since this genus contains a broad range of equally interesting and conspicuous species, we have decided to describe the *Amanita* taxon in general terms, with emphasis on the type-

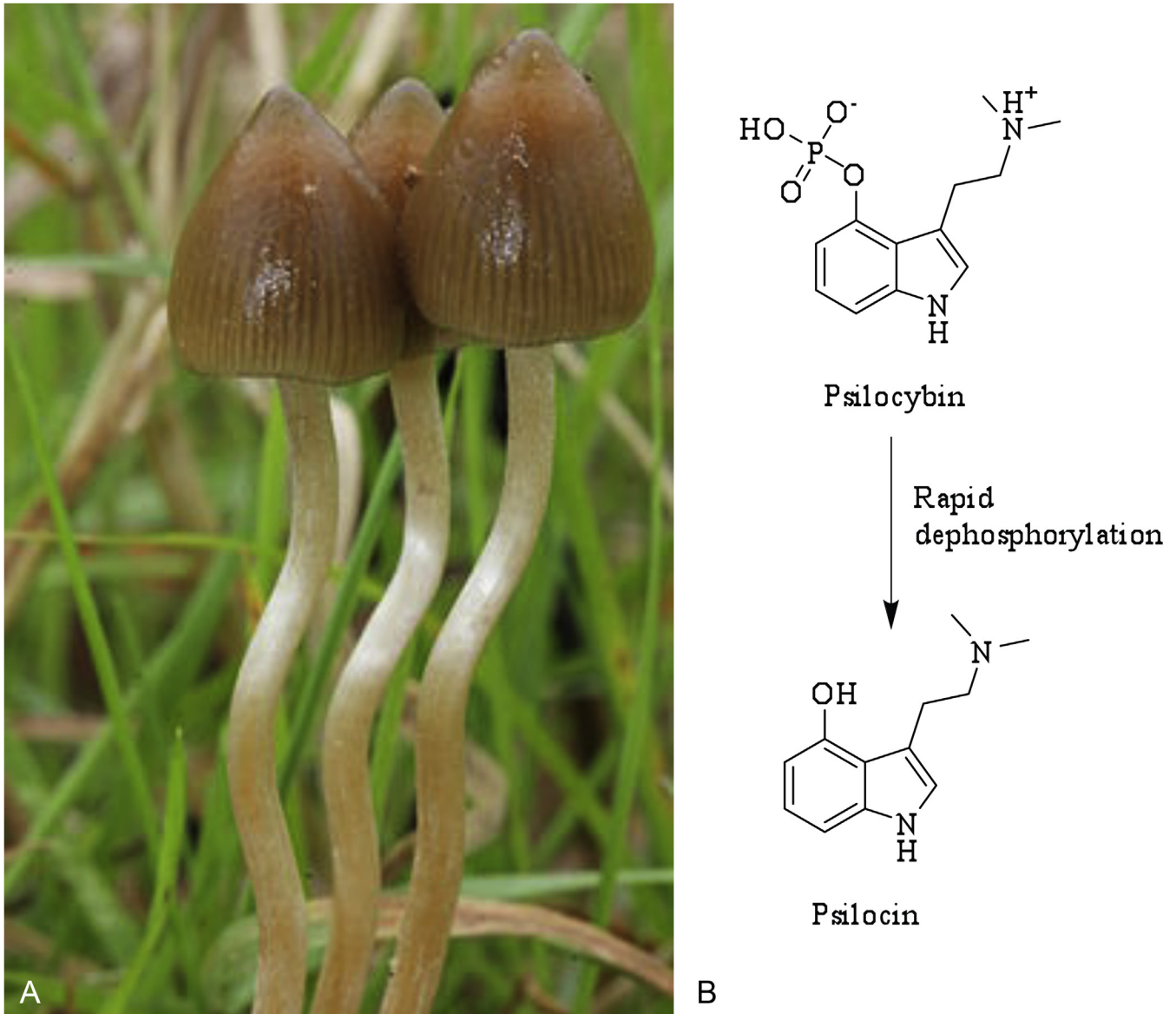


Fig. 7. **A.** *Psilocybe semilanceata* (Copyright © 2012 Alan Rockefeller), commonly known as the liberty cap, is one of many basidiomycetes which produce the metabolite psilocybin. **B.** In the body psilocybin is quickly dephosphorylated into the active compound Psilocin.

species, *Amanita muscaria*. *Amanita muscaria*, the fly agaric, has long been recognised for its acknowledged toxicity, its use for recreational purposes and its insecticidal properties.

Amanita are mycorrhizal in nature, having symbiotic relationships with a wide range of deciduous and coniferous trees, while related genera (*Limacella*, *Saproamanita*) in the family *Amanitaceae* are likely saprotrophic (Redhead *et al.* 2016). Indeed, a recent project that sequenced the genome of *A. muscaria* found that much of the wood-degrading machinery has been lost from this species, likely due to its adaptation to a mycorrhizal life-style (Wolfe *et al.* 2012, Kohler *et al.* 2015). Individual species can often establish interactions with multiple host plants belonging to different taxa (Geml *et al.* 2008); *A. muscaria* for example has been reported to colonise the root environment of birch (*Betula* spp.), as well as that of larch, pine and the Norway spruce, *Picea abies* (Hudson 1986). The basidiocarps formed by fungi of this genus are generally characterised by the presence of annulus, volva, free gills and white spore print, and can be a diverse range of colours (Alexopoulos *et al.* 1996). The most famous representatives of

this taxon include *Amanita caesarea* (Caesar's mushroom), which produces an orange-yellow edible mushroom, the poisonous *Amanita virosa* (the European destroying angel), with a white basidiocarp, as well as the deadly *Amanita phalloides* (the death cap), which produces an olive-green toadstool, and is estimated to cause a striking 90–95 % of all deaths from fungal poisoning in Europe (Litten 1975). The basidiocarps of *A. muscaria* can reach up to 50 cm diameter (Michelot & Melendez-Howell 2003), and can be bright red, orange or yellow, scattered with white scales or patches (Fig. 8A), and can sometimes be mistaken for that of the edible *A. caesarea*. *A. muscaria* owes both its scientific and common names to its documented insecticidal properties against the house fly (*musca* in Latin). The toxicity of the fly agaric, as well as that of the related species *A. pantherina*, is believed to be based upon the activity of two specific toxic compounds: ibotenic acid and muscimol (Takemoto *et al.* 1964, Chilton & Ott 1976). Ibotenic acid is an amino acid analogue of glutamic acid, and once ingested, the low pH of the gastrointestinal tract causes it to be decarboxylated into muscimol (Fig. 8B).



Fig. 8. A. *Amanita muscaria* toadstools demonstrating the range of colours and fruiting body shapes observed for this species. The scales seen on the caps of this species are remnants of the universal veil that surrounds the immature fruiting body (Copyright © Alan Rockefeller). **B.** Toxic compounds produced by *Amanita* fungi. Ibotenic acid and muscimol act as analogues of the amino acid glutamic acid, and the neurotransmitter GABA, respectively. Ibotenic acid is decarboxylated to muscimol in the body. α -amanitin is considered one of the most deadly of the amatoxins, all of which inhibit RNA polymerase.

Muscimol acts as an analogue of gamma-aminobutyric acid (GABA). Both ibotenic acid and muscimol can cause neuronal degeneration by targeting glutamic acid and GABA receptors, respectively (Schwarcz *et al.* 1979, Taira *et al.* 1993).

Looking at the whole taxon, fungi of the genus *Amanita* can produce a wide range of mycotoxins that can be classified into three main groups of cyclic peptides: amatoxins, phallotoxins and virotoxins (Alexopoulos *et al.* 1996). Amatoxins are inhibitors of DNA-dependent RNA polymerase II, leading to impaired gene transcription, a resulting reduction in protein synthesis, and ultimately apoptosis of the cell or necrosis (Buku *et al.* 1971). The structure of α -amanitin, considered to be one of the most deadly of all the amatoxins, is shown in Fig. 8B. Phallotoxins and virotoxins induce polymerisation of G-actin, promoting an anomalous stabilisation of F-actin filaments (Wieland 1977). Beyond their importance as toxins, these natural products from

Amanita species are significant as the first ribosomally synthesised and post-translationally modified peptides (RiPPs) identified from fungi (Hallen *et al.* 2007, Walton *et al.* 2010). RiPPs are a recently recognised class of secondary metabolites that have been gaining significant attention in recent years (Arison *et al.* 2013).

Poisoning by toxic *Amanita* species typically proceeds through four stages post ingestion (Alexopoulos *et al.* 1996). The first stage is a latent phase that can last between 6 and 12 h, where, due to the slow action of the mycotoxins, no symptoms are reported. In the second phase there is appearance of vomiting, diarrhoea, and abdominal pain, which all together can also lead to severe dehydration. The third stage is characterised by a temporary and apparent improvement in the condition of the patient. However, the toxins have by now started inhibiting cellular metabolism. In the fourth stage liver and kidney failure

usually occur, and may be accompanied by internal bleeding due to an altered coagulation capability of the blood. This can lead to death as fast as 6 to 8 d after consumption of the poisonous mushrooms. The outcome of the poisoning depends however on several factors, such as the amount of mushrooms consumed, the health and weight of the consumer, as well as the timing of the medical treatment offered. It should also be noted that each of the *Amanita* species contain its own pool of toxic substances, which may be more or less dangerous for humans. In the specific case of *A. muscaria* poisoning, death is not the usual outcome (Michelot & Melendez-Howell 2003).

The fly agaric has long been known for its psychotropic and hallucinogenic effects, which are believed to be due to the two toxic amino acids mentioned above, ibotenic acid and muscimol (Scotti de Carolis et al. 1969). *Amanita muscaria* usually contains only trace amounts of muscarine, which makes this species an attractive choice for drug consumers. In low concentrations, muscarine can cause unpleasant side effects by mimicking acetylcholine, which include sweating, salivation and pupillary contraction (Bhatnagar et al. 1971). However, in high doses, muscarine can lead to death. It is believed that the recreational use of *A. muscaria* dates back many centuries and spreads across different civilisations, largely being consumed as an entheogen during ceremonies by Siberian tribes (Rolfe & Rolfe 1925), as well as being the basis of a fertility cult in Christianity (Allegro 1970). Wasson hypothesised that soma, a ritual drink consumed in honour of the homonymous Hindu God of the moon, was made using *A. muscaria* extracts (Wasson 1968).

MEDICINAL BASIDIOMYCETES

The medicinal properties of mushrooms have been known about for millennia and were exploited for the benefit of humans by many ancient civilisations, including those in Ancient China, Eastern Europe, Mesoamerica and Africa (Wasser 2011). This tradition has continued into the present day, particularly in China, Korea and Japan, with modern clinical practices involving the use of mushroom preparations. Polysaccharide Kureha (PSK) – a natural product from *Trametes versicolor* – is approved for use in cancer treatment in Japan. Isolated in the 1960s, by 1987 over 25 % of the Japanese expenditure on anticancer agents was spent on PSK (Sullivan et al. 2006), showing the value placed on medicinal mushroom products in certain cultures.

The health promoting activities attributed to mushrooms are many, including antibacterial, antiviral, antiparasitic, anticancer, cardioprotective and cholesterol lowering. For instance, over 200 species of mushroom have been reported to markedly inhibit the growth of various tumours (Wasser & Weis 1999). Although traditionally whole mushroom extracts have been used, some fruiting bodies are scarce and with a greater understanding of natural product science, individual compounds with beneficial pharmacokinetic properties can now be identified and purified.

In this review, we will discuss two basidiomycetes that have contributed to medicine in very different ways: *Ganoderma lucidum*, a fungus which has been used in traditional medicine for thousands of years, and *Clitopilus passeckerianus*, which produces pleuromutilin, the lead compound for the pleuromutilin class of antibiotics.

Ganoderma lingzhi and the *G. lucidum* species complex

Ganoderma lingzhi is a highly revered medicinal mushroom, which has been attributed with a plethora of health benefits and has been used in traditional medicine for thousands of years (Bishop et al. 2015). Belonging to the *G. lucidum* species complex (Zhou et al. 2015), the taxonomy of *G. lingzhi* and related species has only recently begun to be elucidated. Differentiating between the members of the species complex using traditional morphological techniques is problematic, with all species being morphologically similar, and all producing conspicuous fruiting bodies with red, shiny, kidney-shaped caps, the flesh of which are soft and corky (Fig. 9A–B). The advent of sequencing is now allowing a better understanding of the species complex to emerge (Hseu et al. 1996, Zheng et al. 2009), and there are currently considered to be 13 member species found globally (Zhou et al. 2015). There is a growing consensus that the *Ganoderma* species traditionally used in Asian medicine is *G. lingzhi* (Cao et al. 2012, Kwon et al. 2016), and as such a large proportion of the research conducted on the medicinal benefits of *Ganoderma* species will have been conducted using *G. lingzhi*, not the type-species *G. lucidum*. The authors of this review will thus refer to the *Ganoderma lucidum* species complex when referencing previous work, and advise caution when assuming species identity.

The genus *Ganoderma*, which means shining skin, was named by the Finnish mycologist Petter Adolf Karsten in 1881 (Karsten 1881). *Ganoderma* belongs in the *Polyporaceae* family of *Agaricomycetes*, so called due to the presence of many small pores on the underside of the fruiting bodies, which contain the reproductive spores. The generic type-species, *Ganoderma lucidum*, was initially reported from the UK and has since been considered to be distributed globally, although the actual distribution of individual member species is unclear due to the historical taxonomic confusion surrounding this species complex. See Zhou et al. (2015) for a recent study of the global phylogeny of this group of fungi.

Ganoderma lucidum species are known as reishi or man-namtake (10 000-yr mushroom) in Japan and ling zhi (mushroom of immortality) in China, where they are seen depicted in ancient art such as ceramics, paintings and carpets. *Ganoderma* fruiting bodies can even be seen on the facades of the Emperors Palace of the Forbidden City in Beijing (Jones 1998). The use of these mushrooms is not, however, restricted to ancient times. Various products have been developed in the form of powders, teas and dietary supplements and worldwide sales of such reishi extracts have been estimated to exceed \$2.5 billion annually (Li et al. 2013), with sales increasing at 18 % per year (Sudheer et al. 2016).

The medicinal effects attributed to members of the *G. lucidum* species complex are said to include anti-cancer, cardioprotective, immunomodulatory, anticonvulsant, neuroprotective, hypoglycaemic, hepatoprotective, cholesterol lowering, anti-inflammatory, fungicidal, antibacterial and anti-viral, including anti-HIV. Although many of these claims are based on anecdotal evidence, an increasing number are now being demonstrated using more rigorous scientific approaches. Studies using mouse models, for example, have demonstrated the hypoglycaemic (Xiao et al. 2012) and LDL-cholesterol lowering (Oluba et al. 2012) effects of *Ganoderma* extracts. One study using rats

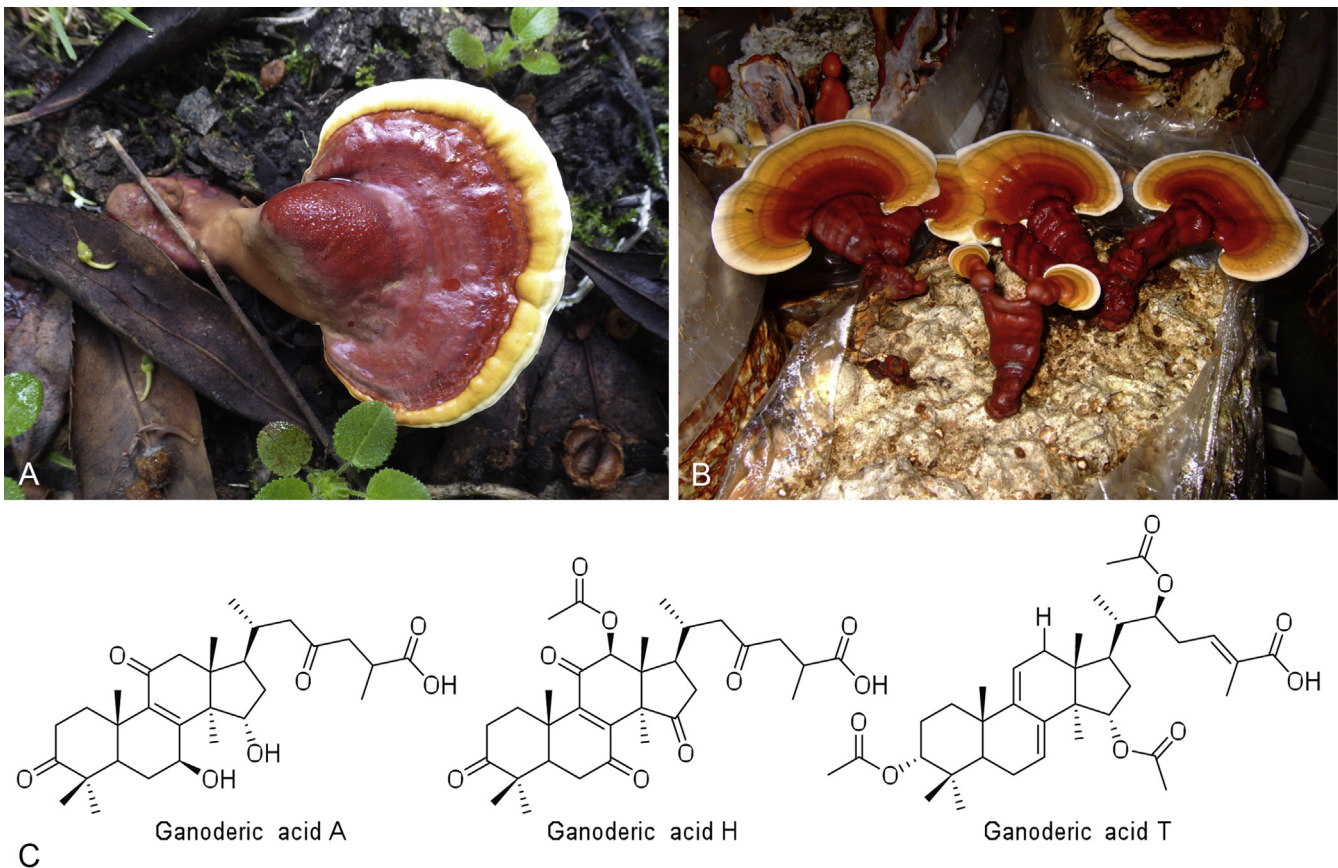


Fig. 9. A–B. The brightly coloured kidney shaped basidiocarp of *Ganoderma lucidum* species, in the wild (A: Copyright © zaca) and in cultivation (B). C. *G. lingzhi* produces a wealth of active secondary metabolites including hundreds of ganodermic acids. Ganoderic acids A and H have been shown to suppress the growth and spread of breast cancer (Jiang *et al.* 2008). Ganoderic acid T has been shown to induce mitochondria-mediated apoptosis in lung cancer cells (Tang *et al.* 2006).

found that *Ganoderma* extracts enhanced the activity of heart mitochondrial enzymes and respiratory chain complexes, partially ameliorating the age-related decline in cellular energy production (Sudheesh *et al.* 2009). The most widely studied aspects of *G. lucidum* species, however, are the immunomodulatory and anti-cancer properties.

The effects of *Ganoderma* species on a wide range of cancers have been investigated, including leukaemia, bladder cancer, breast cancer, cervical cancer, colon cancer, hepatoma and gastric carcinoma. A meta-analysis concerning the overall efficacy of extracts found that when used in conjunction with chemotherapy, the outlook for cancer patients was significantly improved and immune stimulation was observed (Jin *et al.* 2012). However, it also concluded that *Ganoderma* extracts are not suitable as a first-line treatment for cancer, as when used alone no significant effect on tumour size could be demonstrated.

The mechanisms behind the observed anti-cancer effects are complex and multiple. Different studies have identified different mechanisms, and the contribution of individual mechanisms is likely to vary depending on the chemical composition of the extract used and the type of cancer. A recent review, which analysed over 270 patents and peer-reviewed articles concluded that the anti-cancer effects of *Ganoderma* were due to a combination of at least five different mechanisms: (1) activation/modulation of the immune response of the host, (2) direct cytotoxicity to cancer cells, (3) inhibition of tumour-induced angiogenesis, (4) inhibition of cancer cell proliferation and metastasis and (5) deactivation of carcinogens (Boh 2013).

Significant work has been done towards identifying the specific bioactive compounds of *Ganoderma lucidum* species. To

date over 300 bioactive compounds have been detected from fruiting bodies, including fatty acids, nucleotides, polysaccharides, glycoproteins, sterols, steroids, proteins, peptides and triterpenoids (Xia *et al.* 2014). Peptidoglycans, polysaccharides and triterpenoids have attracted particular attention as the major physiologically active constituents. For example, *G. lucidum* proteoglycan (GLPG) has been shown to exhibit antiviral activity against type 1 and type 2 herpes simplex virus (Li *et al.* 2005). Specific polysaccharides have demonstrated antitumour (Miyazaki & Nishijima 1981), hypoglycaemic (Hikino *et al.* 1985, Tomoda *et al.* 1986) and immunological (Bao *et al.* 2001) activities. The anticancer effects of *G. lucidum* triterpenoids (GLTs), of which over 140 have been isolated and characterised (Wu *et al.* 2013a), have been repeatedly demonstrated using both *in vitro* and *in vivo* studies. For example, ganoderic acid T has been shown to induce mitochondria-mediated apoptosis in lung cancer cells, and has therapeutic potential as an agent against high metastatic lung carcinoma (Tang *et al.* 2006, Xu *et al.* 2010). Ganoderic acids A and H have been shown to suppress both the growth, and invasive behaviour of human breast cancer cells (Jiang *et al.* 2008) (Fig. 9C).

In nature, *Ganoderma lucidum* species grow as saprotrophs at the base, or on stumps, of deciduous trees, particularly maples. *Ganoderma lucidum* species are widely, though not abundantly, distributed, being found in tropical and subtropical climates on various continents, including Europe, North and South America and Asia (Zhou *et al.* 2015). Due to the natural scarcity of *Ganoderma* fruiting bodies, and the increased demand for *Ganoderma* extracts, various cultivation methods have been developed. The specific variables favoured for cultivation

depend on the species or isolate used and also the desired product. For example, classical basidiocarp cultivation techniques have been applied, using substrates such as grain, sawdust and wood logs (Erkel 2009, Cilerdzic *et al.* 2014). However, this process is very time-consuming, so an alternative approach uses submerged fungal cultures, which produce only the vegetative fungal mycelia. This has been demonstrated as a promising approach for the production of various compounds including polysaccharides (Fang & Zhong 2002, Wagner *et al.* 2003, Habijan *et al.* 2015). Genetically engineering strains to increase the production of ganodermic acids in submerged cultures has also enjoyed some success (Zhou *et al.* 2014, Xu *et al.* 2015, Li *et al.* 2016). As well as being a faster approach, the use of submerged cultures allows improved control over various fermentation conditions such as nutrient availability, pH and oxygen, which allows optimisation and greater reproducibility. Reproducibility, both in terms of fungal yields, but also the chemical composition of the resulting extracts, will become increasingly important if *Ganoderma* extracts and purified compounds are to become recognised and regulated medicinal products. The development of such specific bioactive compounds as targeted therapeutic agents would be a great step forward for *Ganoderma* research.

In 2012, two research groups simultaneously published draft genomes for *G. lucidum* of 39.9 Mb (Liu *et al.* 2012) and 43.3 Mb (Chen *et al.* 2012). A rich array of genes linked to secondary metabolite biosynthesis were revealed, including P450s, regulatory genes and transporters (Chen *et al.* 2012) and a putative ganodermic acid pathway has been proposed (Liu *et al.* 2012). Both groups also recognised the presence of a diverse set of wood degrading enzymes, as is fitting with the white rot lifestyle of *Ganoderma lucidum* species.

Clitopilus passeckerianus

Clitopilus passeckerianus may not be as publically well known as most of the species described in this review. However, it was included here for being the only basidiomycete to date to produce an antibiotic that has led to the generation of commercial derivatives, which are successfully used both in human and veterinary medicine.

Clitopilus passeckerianus is an Agaricales of the taxon *Entolomataceae*, a family that contains more than 1 500, predominately saprotrophic, species (Co-David *et al.* 2009). As with other species of the *Clitopilus* genus, *C. passeckerianus* is endemic to temperate northern regions, and produces characteristic pink angular spores with longitudinal ribs (Co-David *et al.* 2009). Relatively little is known about the general biology of this fungus, although it has been reported as an occasional contaminant of commercial mushrooms beds. What is presently understood is that the isolate of *C. passeckerianus* currently used for the industrial production of pleuromutilin is dikaryotic, as inferred from the production of hyphal knots and mature fruiting bodies (Fig. 10A) (Hartley *et al.* 2009), and the sequencing of multiple alleles for certain genes (Bailey *et al.* 2016).

The first report of antibiotic production in *C. passeckerianus* came in 1951 from Kavanagh *et al.* (Kavanagh *et al.* 1951), who first discovered that two species then classified in the genus *Pleurotus* (now known as *Clitopilus* species), *Pleurotus passeckerianus* and *Pleurotus mutilus*, were producing an

antibacterial substance active on Gram-positive bacteria, and named it pleuromutilin. Despite several reports of production of pleuromutilin from other Agaricales, such as *Drosophila subatrata* (now known as *Parasola conopilus*) (Kavanagh *et al.* 1952), controversy on the taxonomy of pleuromutilin-producing fungi was clarified only recently when eleven pleuromutilin-producing isolates were found to fall within a distinct clade of the genus *Clitopilus* (Hartley *et al.* 2009).

Ten years after its discovery, Arigoni (Arigoni 1962) and Birch (Birch *et al.* 1966) independently unveiled the chemical formula of pleuromutilin (Fig. 10B), also proving its diterpene nature. Although pleuromutilin itself has modest antibacterial activity and has not been used as a commercial antibiotic, extensive structure–activity relationship studies have been done on more than 1 200 semi-synthetic derivatives with the aim of enhancing MIC and improving pharmacokinetic properties (Novak 2011). This led first to the commercialisation of two pleuromutilin-derived antibiotics employed in veterinary field: tiamulin (Sandoz) (Drews *et al.* 1975) and valnemulin (Novartis) (Aitken *et al.* 1999), both used on swine and poultry as a treatment and prophylaxis agent for dysentery caused by Gram-positive bacteria and *Mycoplasma* spp. infections. In 2007 the first pleuromutilin antibiotic was approved for the use in human medicine, retapamulin (GlaxoSmithKline) (Rittenhouse *et al.* 2006), and has since been used as a topical treatment for impetigo skin infections, typically caused by Gram-positive bacteria like *Staphylococcus aureus* and *Streptococcus pyogenes*. Research is still ongoing to develop novel pleuromutilin derivatives that could be employed as systemic antibiotics in human medicine (Ling *et al.* 2014, Zhang *et al.* 2015). One very promising compound is lefamulin, a pleuromutilin derivative developed by Nabriva Therapeutics that is soon to be entering phase III clinical trials for the treatment of moderate to severe CAPB (community-acquired bacterial pneumonia) (Prince *et al.* 2013, Rubino *et al.* 2015, Waites *et al.* 2016). Fig. 10B shows the structures of pleuromutilin and the various derivatives.

The success of pleuromutilin antibiotics, as the first class of antimicrobial agents produced from a basidiomycete fungus to be commercialised, is partly due to their low potential to induce resistance in targeted bacteria, as seen with retapamulin and the pathogens *S. pyogenes* and *S. aureus* (Kosowska-Shick *et al.* 2006, Rittenhouse *et al.* 2006). Moreover, pleuromutilin antibiotics have a specific mode of action that relies on binding to the 50S ribosomal subunit in bacteria at the level of the peptidyl transferase centre (PTC) (Hodgkin & Högenauer 1974), which shows low cross-resistance with antibiotics having a similar mode of action (Jones *et al.* 2006, Williams *et al.* 2007).

The rising need for new antibiotics and the full exploitation of those already known, means increasing attention has been paid to pleuromutilin and its producing organism in recent years. Firstly, studies were conducted with the aim of enhancing antibiotic titres from *C. passeckerianus* by the traditional approach of random mutagenesis (Papa *et al.* 2006). The biosynthetic pathway to the antibiotic was proposed by Tsukagoshi *et al.* (2007) based on the results of feeding experiments with isotopically labelled predicted intermediates. Total synthesis has been achieved, so far adopting three different strategies, as reviewed by Fazakerley and Procter (Fazakerley & Procter 2014), however so far these have always resulted in low production yields that could not be translated

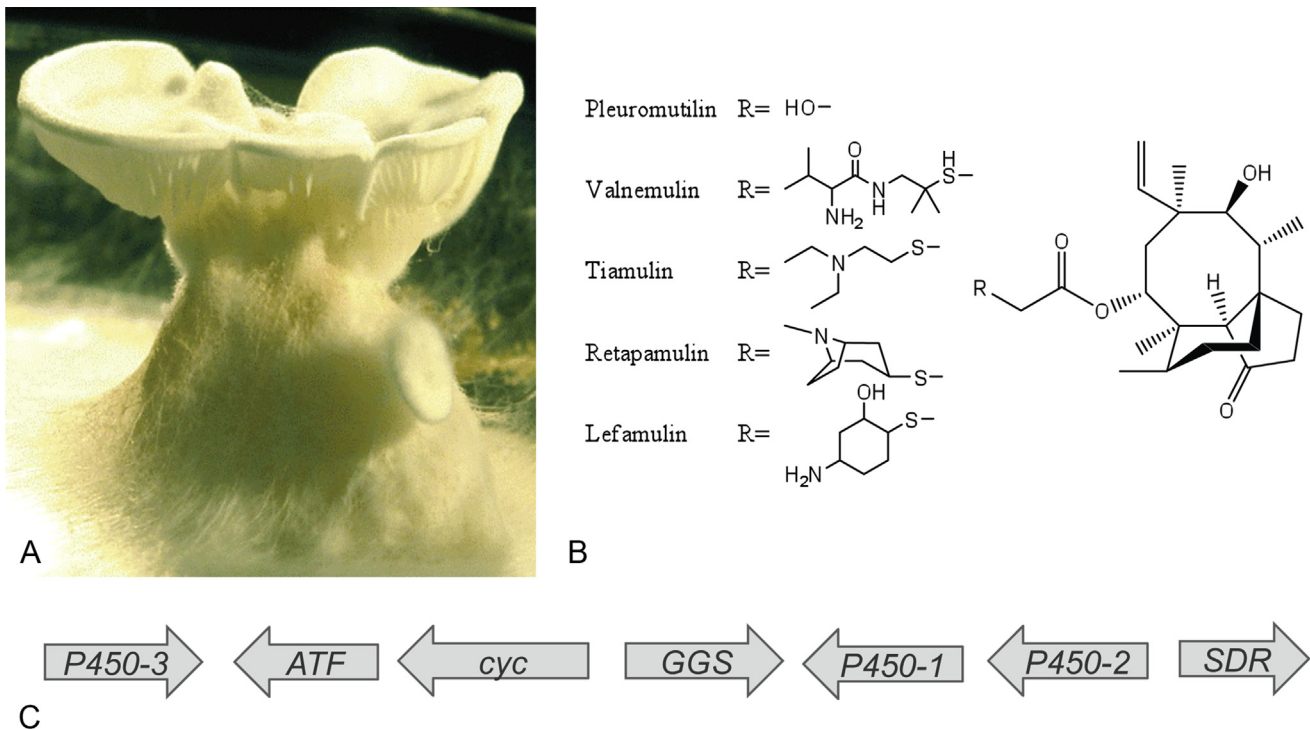


Fig. 10. A. A fruiting body of *Clitopilus passeckerianus*, the pleuromutilin producing basidiomycete (Photograph taken by Tim Colborn). **B.** The chemical structure of pleuromutilin, the natural product, and the various pleuromutilin derivatives. **C.** The pleuromutilin gene cluster, recently identified by Bailey *et al.* (2016), contains the seven genes required to biosynthesise the antibiotic pleuromutilin: A geranylgeranyl disphosphate synthase (GGs), a cyclase, (*cyc*), three cytochrome P450s, an acetyl transferase (ATF) and a short-chain dehydrogenase/reductase (SDR).

into an industrial route of production. A protocol for the transformation of *C. passeckerianus* has been established (Kilaru *et al.* 2009a), and subsequent attempts to increase pleuromutilin production through genetic engineering of the native host have met with some success (Bailey *et al.* 2013a). Finally, the most recent publication has reported the discovery of the pleuromutilin biosynthetic gene cluster of *C. passeckerianus* (Fig. 10C) and exploited it in a heterologous system to establish increased production titres (Bailey *et al.* 2016).

It is worth noting that the various bioactivities demonstrated by fungal natural products, such as antibacterial, antiviral, and antifungal can be harnessed not only for medical purposes, but also to protect crop species from disease and therefore play an important role in food security. The strobilurins for example, are a class of antifungal compounds first isolated from the basidiomycete species *Strobilurus tenacellus*. First launched in 1996, the strobilurins quickly became one of the most important classes of agricultural fungicides (Bartlett *et al.* 2002).

SYMBIOTIC BASIDIOMYCETES

Symbiotic relationships are found across all Kingdoms of life and are vital to the healthy functioning of ecosystems. Mycorrhizal fungi, which form close symbiotic associations with plants, are a perfect example of this. They colonise their host's roots, either intracellularly as arbuscular mycorrhizal fungi, or extracellularly as ectomycorrhizal fungi. In these relationships the plant provides the fungus with sugars produced by photosynthesis and in return the fungus provides the plant with various nutrients such as nitrogen and phosphorus. The fungi also play a vital role in protecting the plants from pollutants, for example by retaining heavy metals. As a result of this interaction, mycorrhizal plants

have an increased growth rate and are less susceptible to various stress factors (Feng *et al.* 2002, Schützendübel & Polle 2002, Woodward *et al.* 2012). This plant/fungal partnership is thought to have been essential for the early colonisation of land by plants. The surprising ability of endophytic fungi to colonise genetically divergent crop species forms the basis of symbiogenic technology, where seeds or seedlings are inoculated with fungi that then confer fitness benefits to the crops. This technology is increasingly being developed and applied as a way of sustaining agricultural productivity in the face of 21st century climate change (Woodward *et al.* 2012).

Many of the species discussed in this review form mycorrhizal relationships with plant species, including many of the *Amanita* mushrooms, but in this section we will specifically discuss *Laccaria bicolor*. *L. bicolor* has been intensively studied and being the first ectomycorrhizal fungus to be fully sequenced, this species has become the basis for much of our understanding of these fascinating symbiotic fungi.

For our second species, we have chosen *Leucoagaricus gongylophorus*, an intriguing species that has an obligate mutualistic relationship with many different species of leaf-cutter ants. This is one of a number of fascinating symbiotic relationships basidiomycetes have with insect species. Others include *Amylostereum areolatum*, a white rot basidiomycete that provides digestive enzymes to wood wasps (Kukor & Martin 1983) and *Septobasidium retiforme*, which infects scale insects, obtaining nutrients that the insects get from plant sap and in return forming protective chambers in which the insects are housed (Paracer & Ahmadjian 2000).

Laccaria bicolor

Laccaria bicolor is a mycorrhizal symbiont that forms ectomycorrhizal associations with a range of tree species including varieties

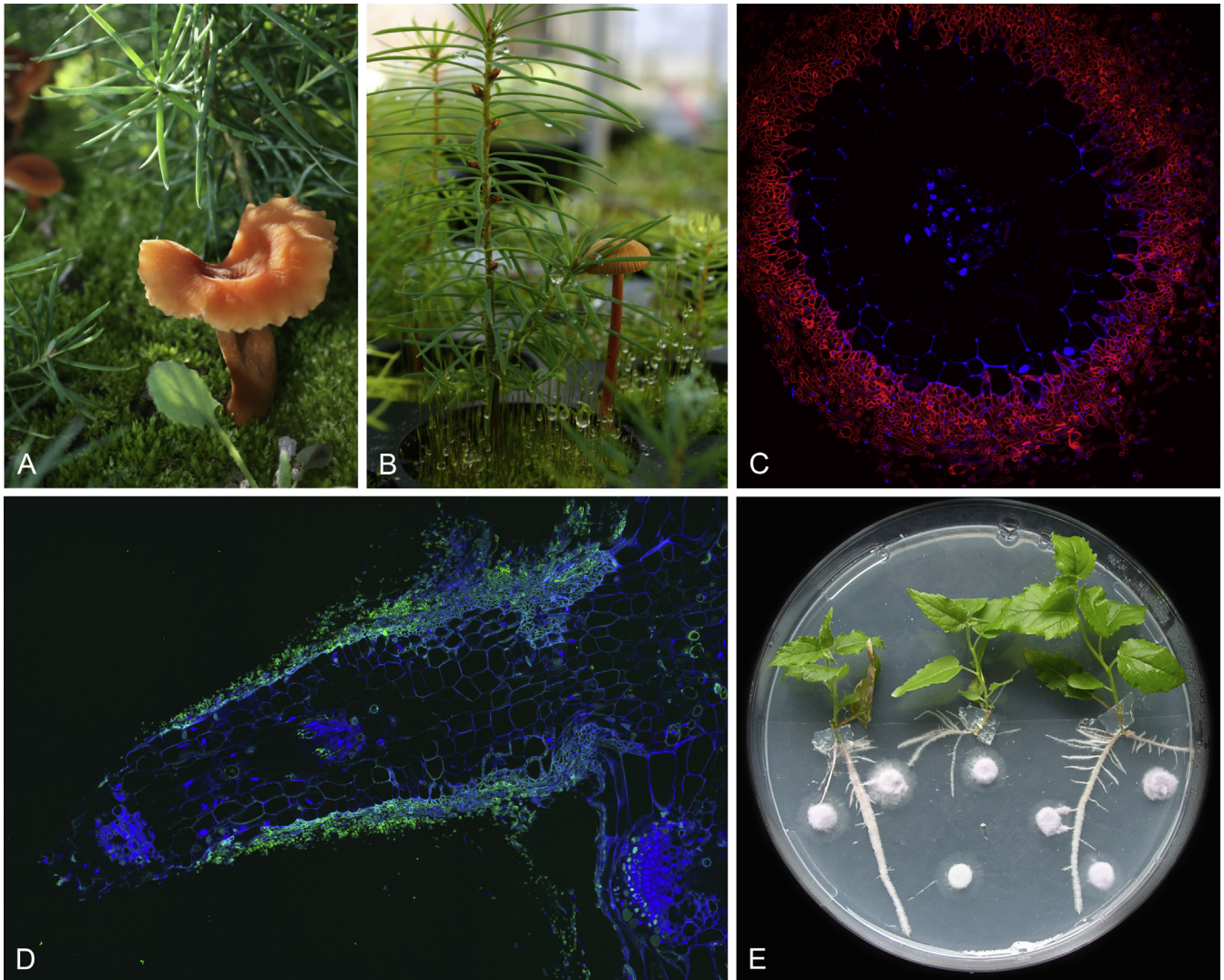


Fig. 11. A–B. *Laccaria bicolor* growing as a mycorrhizal association with Douglas fir, showing fruiting bodies in nursery bed (A) and greenhouse (B) conditions. C–D. The fungus grows as an extensive mycelial network (called the mantle sheath) surrounding the root, with occasional mycelial ingrowths between cells of the root epidermis: the so-called Harting net. A transverse section (C) and longitudinal section (D) of colonised Poplar, stained with DAPI and WGA633. E. Colonisation of the root can be observed under laboratory conditions (colonisation of *Poplar* seedling roots on agar plates) where typically the roots show reduced extension and extraradical hyphae can be seen growing from the mantle out into the surrounding media. Images courtesy of Francis Martin, Feng Zhang, Aurélie Deveau and Anne Jambois, INRA.

of birch, pine and spruce (Podila *et al.* 2002). *L. bicolor* forms small tan-coloured basidiocarps with lilac gills, which dull on ageing and can be found near the base of symbiotic tree species (Fig. 11). This tendency for the colours to fade has led to the common name of “deceiver” as the faded hues lead to difficulties in identification. The preferred habitat of the fungus is temperate, boreal forest, primarily in Northern Europe and North America (Mueller & Gardes 1991, Mueller 1992, Baar *et al.* 1994, Plett *et al.* 2012).

Typically for basidiomycetes, the life cycle of *L. bicolor* is comprised of a monokaryotic and a dikaryotic stage and it is the dikaryotic stage which dominates in vegetative growth and generally forms the symbiotic relationship (Kropp 1997). Both ploidy states are capable of indefinite growth, which facilitates maintaining cultures for scientific study. *L. bicolor* is also capable of a dual saprotrophic and biotrophic lifestyle, capable of growing both freely in the soil and in living roots. This dual lifestyle means that unusually for an ectomycorrhizal fungus, *L. bicolor* can be maintained in a pure culture before co-cultivation with roots of mycorrhizal partner trees in order to study the interactions (Iwase 1997, Siri-in *et al.* 2014), making it an ideal model for studying mycorrhizal fungi. An *Agrobacterium*-mediated transformation

system has also been established for *L. bicolor* allowing further exploration and understanding of this ecologically important species (Kemppainen *et al.* 2005).

Laccaria bicolor was the first mycorrhizal mutualistic symbiont to have its entire genome sequenced, which was completed in 2008 and revealed a genome size of 65 Mbp (Martin *et al.* 2008, Martin & Selosse 2008), at the time the largest fungal genome to be sequenced. The large size is thought to be partly due to an expansion in gene families allowing for the adaptation to multiple complex lifestyles. An analysis of the genome sequence, along with transcriptomic data, revealed various insights into mycorrhizal symbiosis. A large array of small-secreted proteins (SSPs) were identified, several of which were expressed exclusively in symbiotic tissues (Martin *et al.* 2008). The most highly expressed SSP, mycorrhiza-induced SSP 7 (MiSSP7), has now been well characterised and shown to be necessary for the establishment of the symbiotic association. MiSSP7 is secreted by *L. bicolor* and is targeted to the plant nucleus where it alters the transcription of the plant cell (Plett *et al.* 2011, Plett *et al.* 2012). Interestingly, it does not do this directly, but by interacting with a plant protein, JAZ6, which is a negative regulator of jasmonic

acid (JA)-induced gene regulation. In this way, *L. bicolor* inhibits the plants JA-mediated defence signalling, allowing colonisation to occur (Plett *et al.* 2014).

Genome analysis of *L. bicolor* also identified an increased potential for nitrogen uptake when compared to other basidiomycetes, with a relatively large number of secreted proteases and a higher than average number of transporters, including ammonia transporters. This is consistent with the role of the fungus in supplying the plant host with nitrogen (Lucic *et al.* 2008).

Slightly surprisingly, like *A. muscaria* discussed earlier, genome sequencing has uncovered a reduced enzymatic capability in *L. bicolor*, which lacks the degradation enzymes required for the breakdown of carbohydrates in plant cell walls (Martin *et al.* 2008). However, unlike in the case of *A. muscaria*, this has not led to an obligatory symbiotic life-style. *L. bicolor* does appear to have the enzymatic capacity to metabolise non-plant (bacterial and animal) cell wall polysaccharides (Martin *et al.* 2008) and the ability to use nitrogen of animal origins, which probably contribute to its ability to live as a saprotroph as well as a biotrophic symbiont. This is compatible with reports that *L. bicolor* is capable of carnivory, and has been found to target springtails. The fungus is thought to produce a toxin that paralyses the insects, immobilising them to allow hyphae to penetrate the exoskeleton of the insect to utilise the nitrogen in the springtail bodies (Klironomos & Hart 2001).

Laccaria bicolor's symbiotic tendencies have long been exploited in both agriculture and horticulture where the fungus is used as a soil inoculant (Selosse *et al.* 1998, Müller *et al.* 2013), and it has also been used to aid reforestation projects by increasing the survival rates of saplings. Such intentional partnering of fungi and plants, a form of symbiogenic technology, is an exciting and rapidly growing field of research.

Leucoagaricus gongylophorus

Leucoagaricus gongylophorus, known as *Attamyces bromatificus* when in its asexual anamorphic state (Kreisel 1972), is a basidiomycete that has an obligate mutualistic relationship with approximately 40 species of leaf-cutter ants found throughout warm-temperate Central and South America and southern North America (Weber 1966, Kooij *et al.* 2014a). The higher attine ants, of the genera *Atta* and *Acromyrmex*, cultivate *L. gongylophorus* by cutting sections of leaves and flowers (Fig. 12A) from various plants to create a subterranean nest: a “fungal garden”, consisting of plant material and *L. gongylophorus* and housing the ant queen and her brood (Fig. 12B). In this mutualism, the ants provide the fungus with nutrition and protection from competitors and pathogens and the fungus produces specialised swollen hyphal tips known as gongyliidia (Fig. 12C) to feed the worker ants and the growing larvae (Weber 1966, Fisher *et al.* 1994a, Aylward *et al.* 2012).

Fungus–ant mutualisms were first described in the late 1800s (Belt 1874, Möller 1893) and are estimated to be at least 50 million years old (Mueller *et al.* 2005, Schultz & Brady 2008), with the specific relationship between *L. gongylophorus* and the leaf-cutter ants evolving around 2–8 million years ago (Mikheyev *et al.* 2010). *Leucoagaricus gongylophorus* and its associated ant species play an important ecological role in nutrient recycling, but with millions of worker ants in one colony, they can also be serious agricultural pests (Fowler *et al.* 1989, Zanetti *et al.* 2014).

Leucoagaricus gongylophorus fungal gardens are actively maintained by the ants, which establish vertical strata in their

gardens (Huang *et al.* 2014). In the middle section of the garden, *L. gongylophorus* produces the gongyliidia that contain laccases, proteases, pectinases, hemicelluloses, cellulases and xylanases for digestion of plant tissues and are ingested by the ants and their larvae. The top of the garden contains limited fungal biomass and it is here that the ants add new plant material, masticating it into smaller fragments and depositing faecal fluid containing the fungal-derived digestive enzymes from the ingested gongyliidia to facilitate degradation (Grell *et al.* 2013, Huang *et al.* 2014). The ants also inoculate new plant material with fragments of mycelium from the older, lower part of the garden to expedite digestion. In the lower strata of the garden, ants remove the spent plant material and there is complete turnover of substrate over a 4–6 wk period (Aylward *et al.* 2013, Grell *et al.* 2013).

The fungus is unable to suppress microbial competitors and pathogens itself: excised fragments of fungal gardens and detached fruiting bodies are quickly overcome by other microorganisms (Fisher *et al.* 1994b, 1996). Instead, the ants attempt to maintain the nest axenicity by licking the plant material to sterilise it prior to integration into the fungal garden, “grooming” the fungus garden to remove spores of fungal pathogens including *Trichoderma* and *Escovopsis* to prevent contamination and “weeding” the fungal garden when pathogens are established by removing sections of the nest containing hyphae from species other than *L. gongylophorus* (Currie & Stuart 2001, dos Santos Reis *et al.* 2015). *Acromyrmex* ant colonies go even further to preserve their monoculture and will strive to maintain a specific strain of *L. gongylophorus*: the queen will carry fragments of the old nest containing *L. gongylophorus* when she is establishing a new colony and cultivate a new fungal garden consisting of the same specific strain. *Leucoagaricus gongylophorus* can reproduce sexually, but the ants endeavour to maintain its asexuality through suppressing basidiocarp formation by biting emerging primordia, and any basidiocarps that do form are hollowed out from the inside by the ants, preventing maturation and ensuring no basidiospores are formed, facilitating retention of their preferred fungal isolate (Fisher *et al.* 1994b, Kooij *et al.* 2015a). Mature basidiocarps can be observed within fungal gardens farmed by *Atta* species, suggesting that these ant species are not as meticulous about strain maintenance (Fig. 12D).

In recent years, genomic (Aylward *et al.* 2013, De Fine Licht *et al.* 2013), transcriptomic (Grell *et al.* 2013) and proteomic data (Kooij *et al.* 2014b, Aylward *et al.* 2015) has greatly advanced our understanding of the association between *L. gongylophorus* and the leaf-cutter ants. The genome of *L. gongylophorus* was recently sequenced from a strain isolated from an *Atta cephalotes* leaf-cutter ant colony in Gamboa, Panama (Aylward *et al.* 2013). 101 Mbp of total sequence was generated as a draft genome, suggesting that *L. gongylophorus* has a relatively large genome for a basidiomycete. Combining the sequence data with metaproteomic data for fungal gardens of *Atta cephalotes* and *Acromyrmex echinatior* colonies produced a detailed picture of not only the enzymatic capabilities of *L. gongylophorus*, but also how these are applied to biomass degradation within the fungal gardens (Aylward *et al.* 2013). 145 lignocelluloses were identified, in addition to many pectinases, xylanases, amylases and cellulases. Distinct enzymatic cocktails were identified in the different strata of the fungal garden, for example with certain cellulases being increasingly present in the lower strata, suggesting that these enzymes come into play once the more yielding polymers have been consumed. This analysis also provided further evidence for the role of fungal enzymes in



Fig. 12. **A.** *Atta sexdens* workers carrying leaves back to their colony in Gamboa, Panama. **B.** One year old *Atta colombica* colony with queen on top in Gamboa, Panama. **C.** Gongylidia of *Leucoagaricus gongylophorus* – specialised swollen hyphal tips, which are the principal food source for ant larvae. Bar: 40 μ m. Reprinted from Fisher *et al.* (1994b), with permission from Elsevier. **D.** Colony of *Atta cephalotes* collected in Gamboa, Panama, with *L. gongylophorus* fruiting body. (Photographs A, B and D were kindly provided by Pepijn Kooij of the Royal Botanic Gardens, Kew).

detoxifying plant secondary metabolites, as had been suggested previously (De Fine Licht *et al.* 2013).

Research is ongoing to resolve the phylogeny of the *Leucoagaricus* genus, which appears to be polyphyletic (Johnson 1999, Vellinga *et al.* 2003, Kooij *et al.* 2014b, Pereira *et al.* 2015), and to decipher the specific relationships of the leaf-cutter ant genera with their fungal symbiont, as there are some indications that *Atta* and *Acromyrmex* are cultivating different clades of *L. gongylophorus* (Mikheyev *et al.* 2010, Kooij *et al.* 2015a, b).

PATHOGENIC BASIDIOMYCETES

As well as containing many species that play vital roles as symbionts, the basidiomycete fungi include many pathogenic species, infecting a wide range of hosts and often having devastating effects on hosts in terms of mortality and loss of crop yields. Basidiomycete pathogens primarily infect plants, both monocotyledonous and dicotyledonous, infecting species of both agricultural and horticultural importance.

The first pathogenic species to be discussed in this review is the major plant pathogen *Armillaria mellea*, which has a broad host range, spanning from broadleaf trees to grapevines, and is found widely distributed across the Northern hemisphere, causing significant damage to wild, crop and ornamental species. We also consider *Moniliophthora perniciosa*, the causal agent of Witches Broom Disease, a pathogen of the cocoa tree, which is currently limited to Central and South America, but which has the potential to threaten cacao production worldwide.

Armillaria mellea

Armillaria mellea (*Physalacriaceae*) (Fig. 13A), commonly known as the honey fungus, is a necrotrophic pathogen that causes Armillaria root disease (Baumgartner *et al.* 2011). With taxonomic descriptions dating back to the 1700s (Vahl 1790), *A. mellea* was believed to be a highly polymorphic pathogen until the species complex began to be unravelled in the late 1970s, revealing approximately 40 described species with lifestyles that range from saprotrophic to pathogenic (Korhonen 1978, Anderson & Ullrich 1979, Rishbeth 1982, Watling *et al.* 1991, Volk & Burdsall 1995). Fungi in this genus produce a range of unique secondary metabolites and are unusual within the basidiomycetes in that their persistent vegetative state is diploid rather than dikaryotic (Korhonen & Hintikka 1974, Shim *et al.* 2006, Misiek *et al.* 2011, Mihail 2015). Most, if not all, *Armillaria* species are bioluminescent, with *Armillaria* being one of three fungal lineages responsible for the 'fox fire' phenomenon that has been described for millennia. Light in the range of 520–530 nm is emitted from the mycelium growing in decaying wood, which can cause the entire forest floor to appear aglow. Bioluminescence is only apparent in hyphae and rhizomorphs and has not been observed in fruiting bodies (Murrill 1915, Ramsbottom 1953, Desjardin *et al.* 2008, Mihail 2015). *Armillaria* mushrooms are edible, although it is advisable to cook them thoroughly beforehand to avoid stomach upsets, and some work has been done toward realising their commercial cultivation (Shim *et al.* 2006).

Armillaria mellea sensu stricto is a virulent pathogen found throughout forest, agricultural and urban environments in Europe, North America and in parts of Asia and Africa. It has an extremely large host range and is an economically important pathogen on many fruit and nut crops in Europe and North America, such as walnut (*Juglans* spp.), stone fruits (*Prunus* spp.), apple (*Malus* spp.) and highbush blueberry (*Vaccinium corymbosum*) (Baumgartner & Rizzo 2001, Prodorutti *et al.* 2009, Thomidis & Exadaktylou 2012, Baumgartner *et al.* 2013, Elías-Román *et al.* 2013). Losses can be substantial: 10 % in infected pear (*Pyrus* spp.) orchards and up to 40 % in infected vineyards in California (Rizzo *et al.* 1998, Baumgartner 2004). *Armillaria mellea* is also a significant pathogen of ornamental species and has been reported from public gardens in South Africa infecting trees such as oak (*Quercus* spp.) and horse chestnut (*Aesculus* spp.) (Coetzee *et al.* 2001) and herbaceous species including *Chrysanthemum* spp., *Cynara* spp. and *Cyclamen* spp. in Europe (Guillaumin *et al.* 1993). Furthermore, a role for *A. mellea* in other tree diseases including chronic oak decline (Denman *et al.* 2010) and ash dieback (Gross *et al.* 2014) has also been suggested, where it is implicated in weakening trees and predisposing them to infection by other pathogens.

Armillaria root disease is spread by foraging reddish-black rhizomorphs, hyphae and through contact with infected roots.

Basidiospores are unimportant in infection and no asexual reproductive stage is known (Mwenje *et al.* 1998, Rizzo *et al.* 1998, Hood *et al.* 2008). To penetrate plant roots, rhizomorphs grow appressed to the root surface and produce lateral branches that secrete an assortment of cell wall degrading enzymes such as laccases, pectin lyases, peroxidases, polygalacturonases and suberinases (Mwenje & Ride 1999, Baumgartner *et al.* 2011, Ross-Davis *et al.* 2013). After penetrating the root, hyphae subsequently spread through the phloem and secondary xylem in parallel to the cambium and colonise the surrounding tissues, growing as a mycelial fan through the roots and causing necrotic lesions (Fig. 13B). Infected plants display symptoms that allude to a reduced root system including wilting, early senescence, leaf abscission, dieback and rapid onset of death, with healthy mature trees often succumbing to infection within a few years. The presence of fruiting bodies at the base of diseased trees, internal mycelial fans, epiphytic rhizomorphs (Fig. 13C) and disease centres characterised by dead trees in the centre (Fig. 13D) are indicative of severe Armillaria root disease (Baumgartner & Rizzo 2002, Brazee & Wick 2009). After the death of the host plant, *A. mellea* remains viable in residual roots and stumps in soil for decades, feeding saprotrophically until the area is replanted, at which time new infections are initiated. It is this saprotrophic ability, together with a broad host range, that makes control of Armillaria root disease especially challenging (Baumgartner & Rizzo 2002, Guillaumin & Legrand 2013), particularly if planting orchards or vineyards on land recently cleared of forest trees.

Conventional control methods for Armillaria root disease include the use of fungicides and soil fumigants, but these chemicals are being phased out globally, are expensive and often not completely effective (West & Fox 2002, Baumgartner *et al.* 2011, Percival *et al.* 2011). Cultural management practices consist of root collar excavation (Baumgartner 2004, Percival *et al.* 2011) and removal of residual roots prior to replanting in infected areas. The latter of these is particularly effective but laborious and expensive (Cleary *et al.* 2013). Biological control treatments including the use of bacterial soil inoculants and antagonistic species such as *Trichoderma* have been trialled (Baumgartner & Warnock 2006, Percival *et al.* 2011), but are yet to progress from the laboratory to use in the field.

Recent advances have provided a variety of genetic and molecular tools for *A. mellea*, including a genome sequence (Collins *et al.* 2013) which has revealed a 58.35 Mb genome, proteomic and transcriptomic data (Collins *et al.* 2013, Ross-Davis *et al.* 2013), an *Agrobacterium tumefaciens*-based method for transformation of basidiospores (Baumgartner *et al.* 2010) together with a system of producing basidiospores *in vitro* (Ford *et al.* 2015) and expression of fluorescent proteins GFP and mRFP (Ford *et al.* 2016a). A new infection assay for *A. mellea* using herbaceous plants under controlled conditions has also been recently reported (Ford *et al.* 2016b). These developments should lead to a more comprehensive understanding of *A. mellea* virulence factors and infection strategies to enable the establishment of robust management practices for this pathogen.

Moniliophthora perniciosa

Moniliophthora perniciosa, previously classified as *Crinipellis perniciosa*, is a pathogen of the cocoa tree (*Theobroma cacao*)



Fig. 13. Signs and symptoms of Armillaria root disease. A. *Armillaria mellea* fruiting bodies. B. Mycelial fans underneath bark. C. Rhizomorphs growing from a decaying log. D. An *A. mellea* disease centre in an infected vineyard in California. (Photos courtesy of K. Baumgartner, USDA).

and is the causal agent of “Witches’ Broom Disease” (WBD) (Aime & Phillips-Mora 2005). Different *M. pernicioso* biotypes have been shown to infect a range of plant taxa, including bignoniaceous lianas, solanaceous hosts, and the shrub

Heteropterys acutifolia (Griffith et al. 2003), but it is best known for the huge losses to cocoa crops it causes, with up to 90 % yield losses recorded (Paim et al. 2006). When *M. pernicioso* infection spread in the Bahia region of Brazil in 1989 (Periera



Fig. 14. A–C. The basidiocarps of *Moniliophthora perniciosa* (A: Copyright © Scott Bauer, USDA, Bugwood.org), which form during the wet season, can often be seen emerging from the dead tissues of infected plants (B: Copyright © James A. Saunders, Bugwood.org). The valuable beans of cacao pods are destroyed when the pods are infected with *M. perniciosa* (C: Copyright © Scott Bauer, USDA, Bugwood.org).

et al. 1990), Brazil went from being the third largest exporter of chocolate to an importer (Meinhardt *et al.* 2008). *M. perniciosa* was first reported in the Brazilian Amazon in 1785 and is considered to have evolved in this area. Subsequent recordings of the disease were made in Surinam, Guyana, Ecuador, Trinidad, Colombia and Grenada over the following 200 years, revealing the spread of the pathogen through Central and South America. *M. perniciosa* is currently thought to be restricted to the Americas and to date there have not been any reported cases of the disease in *T. cacao* crops grown in West Africa or South East Asia (Meinhardt *et al.* 2008).

Moniliophthora perniciosa is unusual for a plant pathogen in that it has a hemibiotrophic nature and requires young, living, green shoots to maintain pathogenicity. It is also able to directly infect aerial parts of plants – a trait that is rarely seen in agaricomycete pathogens (Mondego *et al.* 2008). Infection is established when basidiospores infect the active meristematic tissues of the cacao plant. Proposed entry mechanisms have included stomatal entry or entry via wounds or sheared trichomes (Frias *et al.* 1991, Silva & Matsuoka 1999), but it has also been suggested that germ tubes can penetrate leaf surface cuticles and may be capable of penetrating directly into the meristems (Sreenivasan & Dabydeen 1989). A recent study (Sena *et al.* 2014) has shown that *M. perniciosa* does indeed display multiple modes of penetration, including through the base of trichomes, via natural openings in the cuticular surface, through stomata, and directly through intact cuticle, with the latter occurring via both mechanical and enzymatic means (Sena *et al.* 2014).

Infection begins with the chaotic proliferation of new shoots due to hypertrophy and hyperplasia of host cells, which produces clusters of shoots known as “brooms” (Chaves & Gianfagna 2006). The brooms are short lived and after 1–2 mo they change from a bright green to brown and remain in the canopy, which lead to the characteristic “witches broom” appearance (Frias *et al.* 1991). Infection of the flower cushions induces ectopic shoots instead of flowers, and can cause small, hardened parthenocarpic (seedless) fruits (Silva *et al.* 2014). Infection that spreads to more mature pods can often be more cryptic, and in some cases, is only discovered on harvesting (Fig. 14A) (Griffith *et al.* 2003). Basidiocarps (Fig. 14B) form during the wet season under highly moist conditions, and small pink mushrooms can be seen fruiting from the dead brooms (Fig. 14C). The

resulting basidiospores are then readily dispersed in the humid canopy conditions of cacao plantations. High humidity is essential for the dispersal of basidiospores, which is usually only over short distances, with dispersal over larger distance believed to result from human actions spreading basidiospores on asymptomatic infected pods (Griffith *et al.* 2003). Typically there is only one disease cycle per rainy season (Maddison *et al.* 1996).

Relatively little is known about the causes of the specific symptoms. It is not fully understood which effects are the result of fungal toxin production within the host tissues and which symptoms are the result of host defence mechanisms. Certain symptoms point towards an imbalance of plant growth regulators, which may be responsible for the loss of apical growth during the primary stages of infection (Mondego *et al.* 2008). However, the switch from the biotrophic, broom producing stage of infection is thought to be triggered by senescence signalling within the host plant (Teixeira *et al.* 2014).

Existing prevention methods include the efficient removal of infected material, with a focus on pruning the brooms. An additional control method is the application of a spray of mineral oil over the ground, which inhibits the sporulation of pruned material on the ground. Phytosanitisation by the frequent removal of sources of inoculum has proved to be the most effective method for disease control (Andebrhan & Furtek 1994). *Moniliophthora perniciosa* is tolerant to many widely used fungicides, even in higher doses, and as a result there are currently no viable chemical control methods for the treatment of WBD (Farquharson 2014). The application of chemical fungicides is also problematic as the disease is located in the aerial canopy. This means that fungicides require spraying over entire canopies. Alternatively chemicals could be applied to the soil and taken up by the cocoa tree root system but this raises concerns over chemical residues in the mature pods and may be environmentally damaging (Rudgard *et al.* 2012).

An alternative approach to tackling the problem of WBD is the cultivation of disease resistant varieties of cocoa tree. Basidiospores exposed to the extracts of more resistant varieties of cocoa exhibited abnormal growth and stunted germination (Evans & Bastos 1980). Field studies have also evaluated the resistance to WBD in flower cushions of *T. cacao*, to identify isolates with disease resistant phenotypes (Silva *et al.* 2014). It

has also been shown that the biological control agent *Gliocladium catenulatum* was effective as an endophytic symbiont, and reduced the incidence of WBD by 70 % in cacao seedlings (Rubini et al. 2005).

Taxonomically, *M. pernicioso* belongs to the *Marasmiaceae* family of basidiomycetes, and has now been shown to be a sister species to *M. roreri* (Evans et al. 2002, Evans et al. 2003, Aime & Phillips-Mora 2005). *M. roreri*, the causative agent of another devastating disease of *T. cacao* crops known as Frosty Pod Rot, is an unusual basidiomycete pathogen which was originally described as a conidia-producing anamorphic ascomycete due to an absence of fruiting bodies (Ciferri & Parodi 1934). Work has now shown that *M. roreri* is in fact a teleomorph basidiomycete that produces abundant meiospores, which are thought to be highly modified probasidia (Evans et al. 2003). *Moniliophthora roreri* and *M. pernicioso* represent an interesting model for the evolution of pathogenicity in fungi, sitting as they do within a taxonomic clade which is dominated by saprotrophic species (Teixeira et al. 2015). Tiburcio et al. (2010) recently demonstrated that *M. pernicioso* and *M. roreri* probably acquired the required genes for pathogenicity by horizontal gene transfer, including a family of necrosis-inducing proteins from *Phytophthora* oomycetes. *Moniliophthora roreri* is a highly invasive species that has been spreading in recent years, and once established, leads to yield reductions of over 80 % (Phillips-Mora et al. 2006, Krauss et al. 2010), further increasing the importance of understanding this unusual taxonomic group.

The genome of *M. pernicioso* was sequenced and published in 2008 and is estimated to have a genome size of 39 Mbp (Mondego et al. 2008). A transformation system had been developed using the PEG-mediated transformation of protoplasts which, along with other molecular tools, opens up the potential for a greater understanding of the pathogenicity mechanisms for this species (Lima et al. 2003, Leal et al. 2010, Santana et al. 2012).

CONCLUSIONS

We hope that this review has highlighted just how crucial the *Agaricomycetes* are. They are an astoundingly diverse group of organisms, which are vital in nature, recycling nutrients and thus allowing ecosystems to function, as well as directly enabling the survival of plant and animal species through symbiotic relationships. Harnessing these various unique traits, for example in bioremediation, environmentally beneficial waste disposal and the production of biofuels, is something that has been expanding as a fascinating and exciting field of research. More directly, basidiomycetes supply us with food and medicine. Even the apparently negative traits of the basidiomycetes, as pathogens and toxic species, have potential uses to human societies, for example as producers of bioactive compounds or biocontrol agents. Understanding such species, particularly the pathogens of important crop plants, is also important for reducing their negative impacts, particularly at a time when global food-security is so important.

Although our understanding of this fascinating phylum has grown hugely in recent decades, we have only just begun to exploit their true potential. As our understanding of the basidiomycete fungi grows, through the study of model organisms, the development of various tools and techniques and the continuing

discovery of novel species, our ability to exploit their unique abilities and characteristics will also grow. Basidiomycetes have the potential to provide us with the next generation of antibiotics, to reduce environmental pollution, and even produce our fuel. They currently represent one of the great untapped resources of nature.

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