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MINI-REVIEW

Cultivation methods and biology of *Lentinula edodes*

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Abstract

In this study, the biological applications of cultivation methods related to cultivar selection, vegetative growth, and reproductive development in *Lentinula edodes* cultivation are briefly reviewed to clarify the current situation and inform future developments. The current cultivars widely used in the main production areas are derived from wild strains distributed in northern Asia. The most effective techniques for cultivar identification are molecular markers identified in two nuclear genome datasets and one mitochondrial genome dataset. The current stage of cultivar breeding is at the junction of Breeding 3.0 (biological breeding) and Breeding 4.0 (intelligent breeding). Plant breeder's rights and patents have different emphases on new breeding variety protection, with the former being the most utilized globally. *L. edodes* is mostly produced on synthetic logs filled with sawdust substrates. Hardwood sawdust comprises approximately 80% of the substrates. The vegetative growth of *L. edodes* on synthetic logs involves two distinct stages of mycelial colonization and browning. Mycelia mainly perform glycolysis, tricarboxylic acid cycle, and respiratory metabolism reactions to produce energy and intermediates for synthesizing the structural components of hyphae in the vegetative colonization stage. Upon stimulation by physiological and environmental pressures after colonization, mycelia trigger gluconeogenesis, autophagy, and secondary metabolism, increase metabolic flux of pentose phosphate pathway, activate the glyoxylate cycle, and accumulate melanin on the surface of logs to ensure growth and survival. Sexually competent mycelia can form hyphal knots as a result of reprogrammed hyphal branching patterns after a period of vegetative growth (which varies by cultivar) and stimulation by specific environmental factors. Under a genetically encoded developmental program, hyphal knots undergo aggregation, tissue differentiation, primordium formation, meiosis in the hymenium, stipe elongation, basidiospore production and maturation, and cap expansion to form mature fruiting bodies. Growers can achieve good fruiting body shape and high yield by regulating the number of young fruiting bodies and adjusting specific environmental factors.

Key points

- *Cultivar selection becomes less with the increasing technological requirement of L. edodes cultivation.*
- *L. edodes mycelia showed different biological events in the mycelial colonization and browning stages.*
- *Specific cultivar breading may be the next milestone in L. edodes cultivation.*

Keywords *Lentinula edodes* · Cultivar breeding · Cultivation technique · Metabolic regularity · Cytological events

Introduction

Lentinula edodes is a white-rot wood-decaying fungus. The majority of decay involves dead logs of broad-leaf trees, mainly from the family Fagaceae in natural habitats (Sierra-Patev et al. 2023). The vegetative mycelia of *L. edodes* mainly grow in the sapwood of dead logs under the bark and can develop into fruiting bodies on the bark surface under suitable physiological and environmental conditions (Kües and Liu 2000; Ogawa and Yashima 2023). *L. edodes* is the most consumed and cultivated mushroom worldwide, reflecting its unique taste, flavor, nutritional value, and

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medicinal properties (Li and Xu 2022; Ahmad et al. 2023). The cultivation of *L. edodes* involves the efficient generation of high-quality and high-yield fruiting bodies by gradually optimizing the substrate, facilities, and environmental conditions to mimic wild cultivation condition. Historically, there have been three major milestones that have shaped *L. edodes* cultivation: the shock method in China, the development of pure culture spawn in Japan, and the synthetic sawdust log method in China (Fig. 1a; Chang and Miles 2004; Mushworld 2005). China and Japan have alternated as the world's largest producers of *L. edodes*, driven by these key milestones (Chang and Miles 2004). Since 2018, China's

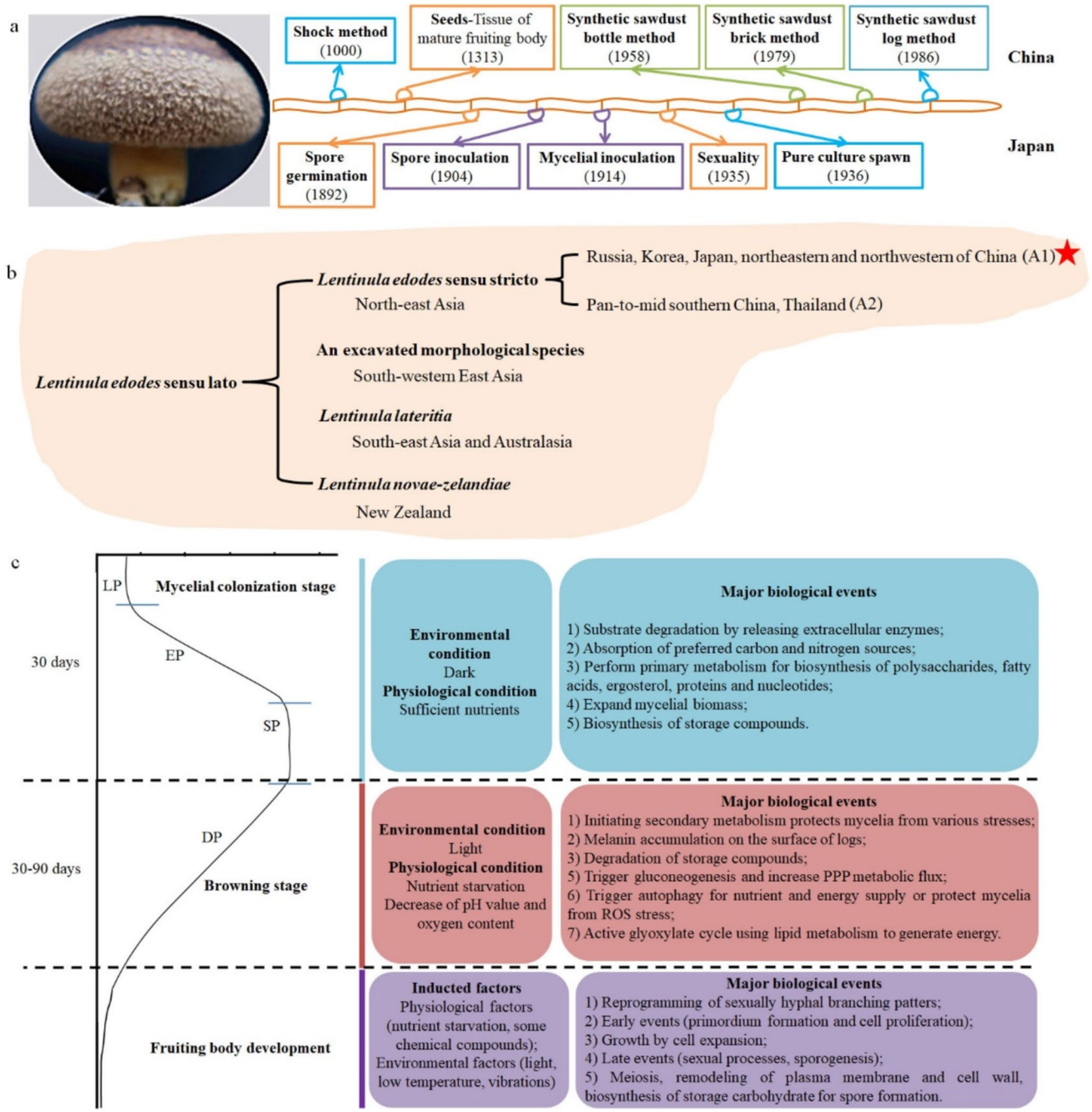

Fig. 1 Major historical events related to *L. edodes* cultivation (**a**), genetic background of cultivars (**b**), dynamic changes of mycelial growth kinetic and major biological events of mycelial colonization stage, browning stage and fruiting body development (**c**). Red five-pointed star refers to the genetic background of current cultivars widely used in main producing area. Mycelial growth curve: LP, lag phase; EP, exponential phase; SP, stationary phase; DP, declining phase. A1 and A2 mean two subgroups of *L. edodes* sensu stricto

annual production of *L. edodes* has exceeded 10,000 million kg, suppling more than 95% of the global output (Zied and Pardo-Giménez 2017; Singh et al. 2020).

Biology is a blend of technological advances and a guiding vision, both essential to the successful development of any science: without the necessary technological progress, the road ahead is blocked, while without a guiding vision, science becomes focused on short-term practical problems with no path forward (Woese 2004). The first major biological advancement that promoted the development of *L. edodes* cultivation was the invention and application of pure culture spawn. In the early and middle stages of the shock method, growers only knew that "gas" in the air and "cloud" in the log were crucial to *L. edodes* cultivation and that tissues from mature fruiting bodies could be used as seeds (Huang 1994). With the advancement of biological knowledge about the life cycle of *L. edodes*, it became clear that "gas" referred to spores and "cloud" referred to mycelia, which represent the sexual and asexual reproduction of *L. edodes*, respectively (Fig. 1a; Huang 1994; Chen 2001). Pure mycelial spawn is a growth medium inoculated with pure mycelial fragments isolated from fruiting body tissue, which can be used directly as seeds without hybridization. The application of pure mycelial spawn not only enabled the cultivation of *L. edodes* in environments different from its natural habit, at but also facilitated the development of new cultivation substrates (Fig. 1a, Chang and Miles 2004; Mushworld 2005). Ultimately, the synthetic sawdust log method was developed based on research into direct fruiting technology using pure culture spawn (Chang and Miles 2004). Biological research has penetrated every stage of *L. edodes* cultivation, and cultivation methods related to cultivar selection, vegetative growth, and reproductive development have been rapidly developed. Here, we briefly review the key results of biological studies conducted exclusively on the cultivation methods of *L. edodes*. The goal of this review is to clarify the current situation and inform future developments to promote the sustainable development of *L. edodes* cultivation science.

Cultivar selection

Genetic background of cultivars

Owing to the constant changes and improvements in species recognition criteria, taxonomic revision is a common feature in current fungal taxonomic literature (Xu 2020). The classification of *L. edodes* has undergone three major changes. The first change is in taxonomic names based on morphological features. The original taxonomic name of *L. edodes* was *Agaricus edodes* by Berkeley in 1877, based on a poor specimen purchased from a shop in Japan (Pegler 1983). With the continued exploration of new morphological features, the designation *L. edodes* was proposed after more than a dozen name changes by different mycologists (Pegler 1983). The second change involves intraspecific taxa based on mating features. Two *Lentinula* species, *L. lateritia* and *L. novae-zelandiae*, have been proven to interfere with *L. edodes*; thus, the three should all be called *L. edodes* according to the naming priority principle (Shimomura et al. 1992). To distinguish between the two *L. edodes* names at different taxonomic levels, the morphological species was named *L. edodes* sensu stricto, and the suggested taxonomic names refer to *L. edodes* sensu lato (Hibbett and Donoghue 1996; Song et al. 2019). The third change involves intraspecific taxa based on the molecular features of certain sequences or genes, especially nuclear ribosomal internal transcribed spacer sequences. An excavated morphological species, two subgroups of *L. edodes* sensu stricto, and two subgroups of *L. lateritia* have been described (Hibbett and Donoghue 1996; Song et al. 2018). As each species concept attempts to capture a few traits, Xu (2020) proposed the genomic species concept that a genome sequence-based classification and identification system could unify and stabilize fungal taxonomy. Tracking the same strains used in many different genomic studies reveals four populations of *L. edodes* sensu lato and two subgroups of *L. edodes* sensu stricto (Fig. 1b; Song et al. 2018; Yu et al. 2022a; Zhang et al. 2022; Sierra-Patev et al. 2023). Different populations and subgroups have specific nuclear and mitochondrial genomic variations related to their geographical distributions (Song et al. 2019; Sierra-Patev et al. 2023). There are currently many hybrids of different populations and subgroups in the field (Song et al. 2018, 2019).

L. edodes cultivars found globally are mainly from two wild subgroups of *L. edodes* sensu stricto. One subgroup is mainly distributed in northern Asia and the other mainly in southern Asia. These were designated A1 and A2, respectively, by Song et al. (2018) (Fig. 1b). Before the invention of pure culture spawn technology, local wild strains were mainly used as cultivars in each cultivation area of each country. For example, Japan primarily uses wild-type strains of A1, whereas China primarily uses wild-type strains of A2. This is because the cultivation area in China (pan-mid-southern provinces) falls within the geographical distribution of A2 (Huang 1994). After pure culture spawns spread to China, many excellent strains were introduced from abroad, especially from Japan (Song et al. 2015). The current cultivars in China have mainly become A1 (Song et al. 2018). With the continuous standardization of cultivation measures and conditions, the sources of cultivars in China are gradually becoming more concentrated and are mainly derived from several excellent cultivars (Ling et al. 2022a). There are two main reasons for this phenomenon. First, *L. edodes* breeding involves screening suitable strains

under relatively unchanged cultivation conditions, rather than changing the cultivation conditions for specific strains. The cost of the latter change is too high. Second, under the current cultivation conditions, A1 strains have better fruiting characteristics (i.e., stable fruiting capacity, high yield, and thick pileus) than other genotype strains (Song et al. 2023). In recent years, China's Yunnan Province has emerged as a special cultivation area for local wild *L. edodes*, which has small fruiting bodies and thin pilei. Its genetic background is not A1, and its seasonal cultivation has obvious geographical distribution selectivity. Additionally, only changing the cytoplasmic genetic background of cultivars may be a good cultivar improvement method for changing the number and quality of fruiting body while ensuring stable fruiting body emergence (Song et al. 2021; Song et al. 2024).

Breeding stage of cultivars

Owing to its long developmental history and rapid development process, plant breeding technology has always been a benchmark for the development of *L. edodes* breeding technology. Based on the techniques involved, plant breeding is divided into five major stages: Breeding 1.0 (experience breeding), Breeding 2.0 (experimental breeding), Breeding 3.0 (biological breeding), Breeding 4.0 (intelligent breeding), and Breeding 5.0 (de novo design breeding) (Wallace et al. 2018; He et al. 2024). The current stage of plant breeding is Breeding 3.0 and will soon reach Breeding 4.0 (Wallace et al. 2018). The developmental stage of *L. edodes* breeding is similar to that of plant breeding, and each stage uses the same technology as plant breeding and a unique technology related to the genetic characteristics of *L. edodes*.

In the Breeding 1.0 stage, growers mainly domesticate wild strains or imported cultivars in the local cultivation environment, equipment, and facilities (Song et al. 2015). In Breeding 2.0 stage, breeders can breed new cultivars by protoplast fusion, mutagenic breeding, and especially by cross breeding (Song et al. 2015; Dong et al. 2022). In contrast to the diploidy (2n) of the plant, the mycelium of *L. edodes* belongs to the heterokaryotic state (n+n), and cross-breeding can occur between two homokaryotic mycelia or between one homokaryotic mycelium and one heterokaryotic mycelium (Song et al. 2015; Auxier et al. 2022). The homokaryotic mycelium does not have specific male or female reproductive organs and can be simultaneously used as the nuclear donor (paternal) and nuclear acceptor (maternal) in one cross-breeding, with the cytoplasm of the cross offspring inherited from the mother (Fukuda et al. 1995). The growth and development of cross offspring in the vegetative and reproductive stages are mainly controlled by the two nuclei, followed by the cytoplasm (Song et al. 2023). The contribution rate of the two nuclei to the formation of mRNA profiles during vegetative growth and reproductive development of the cross offspring is different: one nucleus dominates mRNA production, and the other shows more differentially upregulated genes in important functional groups (Gehrmann et al. 2018; Shen et al. 2024). Homokaryotic mycelia can be obtained from spores and heterokaryotic mycelia (Song et al. 2024). This makes the efficiency of *L. edodes* cross-breeding higher than plant-breeding.

With many molecular markers and genomic data beginning to complement phenotypic data, *L. edodes* breeding has entered the Breeding 3.0 stage; the main breeding technologies are molecular marker-assisted breeding and transgenic breeding. Molecular marker-assisted breeding can avoid and enhance the selection criteria for phenotypes through the indirect or direct selection of genes. Transgenic technology serves to introduce gene sequences for the expression of a desired trait (Visarada et al. 2009; Hasan et al. 2021). Molecular marker-assisted technology has been applied in some areas of *L. edodes* breeding, such as high-throughput nuclear and mitochondrial genotyping, cultivar identification, and the dissection of complex traits with linkage mapping (Gong et al. 2016; Song et al. 2019; Ling et al. 2022a; Yu et al. 2022a). However, compared with plant molecular-assisted breeding technology, the molecular marker-assisted technology of *L. edodes* is still rudimentary, with no involvement yet in areas that include the assessment of parental selection and study of heterosis (Hasan et al. 2021). Transgenic technology has been applicated in many areas of *L. edodes* breeding, particularly for the study and identification of gene functions (Ling et al. 2022b; Wang et al. 2023). However, because of the influence of the stability of genetic transformants, no varieties that have been bred using this method are not yet available. As a core technique of Breeding 4.0, editing breeding can directly modify specific loci in the genome through genome editing tools, such as the CRISPR-Cas9 system, achieving precise changes to target traits (Fang 2024). The CRISPR-Cas9 system has been constructed in *L. edodes* (Moon et al. 2021).

Identification and protection of cultivars

In contrast to many plants that produce new F1 hybrids every year, *L. edodes* cultivars can be expanded by asexual reproduction directly from mycelia or fruiting bodies (Herridge et al. 2019). Additionally, *L. edodes* cultivars have mycelia that have no distinct morphological differences among different cultivars. These two main reasons make the price of *L. edodes* cultivars very low and market circulation very chaotic (Song et al. 2015). Various methods have been used for mushroom identification, including morphological, physical, and chemical detection, instrumental analysis, and molecular biology methods (Wei et al. 2022). Currently, the most effective methods for *L. edodes* cultivar identification are molecular markers based on whole-genome development (i.e., multiple nucleotide polymorphism)

or direct whole-genome sequencing techniques (i.e., genome resequencing) (Ling et al. 2022a, b). Whole-genome sequencing is another method, but it is not suitable for the identification of a large number of cultivars. There are two main reasons for the unsuitability. The first one is the considerably higher cost of sequencing than the cost of resequencing. The second reason is that genomic data cannot be assembled directly based on whole-genome sequencing of cultivars with two nuclei with genetic differences (Shen et al. 2024). In addition, with the discovery of cytoplasmic genetic effects, the mitochondrial genome, the main source of cytoplasmic genetic material in *L. edodes*, has received increasing attention (Song et al. 2019, 2023; Kim et al. 2022). The exact molecular identification of an *L. edodes* cultivar should include genetic information on its two nuclear genomes and one mitochondrial genome.

The plant breeder's right, also known as the plant variety protection system, is the most utilized system globally to protect mushroom varieties (Smulders et al. 2021). As long as a variety is distinct (from all others), uniform (among mushrooms), and stable (across years), it can be sought protection for a period of 20 or 25 years (Bostyn 2021; Smulders et al. 2021). This distinct characteristic means that this variety is distinguished from all others by the expression of at least one of the said characteristics, especially the quantitative traits of fruiting bodies (Bostyn 2021; Deng et al. 2024). Molecular identification techniques are only used as auxiliary markers for plant breeder's rights. The breeder of this variety has the exclusive right to give licenses to others to multiply or use the variety and to charge a license fee on the multiplication or use of the variety for agricultural production (Smulders et al. 2021). Anyone can freely breed new varieties from the first day that it is on the market (Smulders et al. 2021). Another application utilized globally is a patent application for this variety (Smulders et al. 2021). It must be noted that a plant variety, as such, and methods involving classical crossing and selection are exempt from patentability (Smulders et al. 2021). With technical developments such as the use of DNA markers in plant (including mushroom) selection, "natural" traits have become subjects of patent applications; however, the issuance of such patents has been halted by the Enlarged Board of Appeal from 2020, as they may restrict the use of genetic resources for plant breeding (Smulders et al. 2021). Varieties developed using transgenic or editing technology may apply for patent protection (Smulders et al. 2021).

Vegetative growth

Formula of sawdust substrates

The *L. edodes* heterotrophic fungus primarily obtains soluble inorganic and organic nutrients from two types of substrate materials: natural wood logs and synthetic logs filled with sawdust substrates. Synthetic logs filled with sawdust substrates have many advantages over wood logs, such as the high nutrient and taste composition of fruiting bodies, low contamination rate, shortened production time, high yield, and an easily manageable cultivation environment (Chang and Miles 2004; Tabata et al. 2006; Kobayashi et al. 2020; Annepu et al. 2023). Currently, *L. edodes* is mostly produced on synthetic logs filled with sawdust substrates that contain hardwood sawdust, straw, or corncobs as basal ingredients and supplements, such as wheat bran, rice, bran, millet, rye, and maize (Shen et al. 2008). The components and proportions of sawdust substrates significantly affect mycelial growth, primordium formation, yield, fruiting body productivity, and nutritional and medicinal value (Chang and Miles 2004; Xu et al. 2020; Desisa et al. 2023). An accepted standard formula for sawdust substrates is 80% hardwood sawdust and 20% supplements by dry substrate weight, whereas many slight variants have been derived in different countries or places depending on locally available materials (Kilpatrick et al. 2000; Yu et al. 2022b). Thus, oak hardwood and wheat bran may be the best hardwood and supplement, respectively (Ranjbar and Olfati 2016). Higher supplementation levels may increase the yield of *L. edodes*. However, they can also easily promote disease contamination (Kilpatrick et al. 2000). Furthermore, the physical factors of sawdust substrate also greatly affect mycelial growth, yield, and biological efficiency, and some good selection criteria have been screened. The optimal water content of sawdust substrate is that the substrate is filled with free water and lacks bulk water (Wang et al. 2021). A higher weight may increase the yield but decrease the biological efficiency; block shape performs better in small weight, whereas cylindrical shape is better in larger weight (Shen et al. 2008; Hossain et al. 2010).

Two distinct stages

After pure culture spawn is inoculated on the surface or in the inoculation hole of aseptic synthetic logs filled with sawdust substrate after autoclave treatment, the mycelia can migrate from the inoculum to the interior of the sawdust substrate for foraging (Kobayashi et al. 2023a, b). The mycelia of *L. edodes* mainly utilize carbon (i.e., cellulose, hemicellulose, pectin, lignin, and starch) and nitrogen (i.e., proteins) sources from hardwood sawdust and wheat bran to go through the entire proves of vegetative growth (Alzuwaid et al. 2019; Wang et al. 2020). According to the dynamic changes in internal mycelial growth kinetics, surface morphological characteristics, and management conditions of synthetic logs, the vegetative growth process of *L. edodes* has been divided into two distinct vegetative growth stages in production: the mycelial colonization stage (also termed

he spawn running stage, which is approximately 30 days in the dark) and the browning stage (also known as the mycelial maturation stage, which is 30–90 days in light) (Fig. 1c; Song et al. 2023). In the mycelial colonization stage, the mycelia mainly expand the mycelial biomass by continuous apical growth, branching, and fusion, undergo a short lag phase and exponential growth, and reach the stationary phase (Fig. 1c; Jomura et al. 2020; Sánchez and Montoya 2020). In the browning stage, the mycelial growth of *L. edodes* enters a declining phase because of nutrient depletion in the mycelial colonizing area, and mature mycelia on the surface of sawdust-based logs exposed to light accumulate melanin to form a brown film in preparation for fruiting body formation (Fig. 1c; Gonzalez and Aranda 2023; Song et al. 2023).

Biological events in two distinct stages

To facilitate its survival in natural habitats, *L. edodes* has evolved a specific genomic composition of degradative enzymes and fine-tuned and hierarchical metabolic regulatory systems to efficiently sense and utilize available nutrients (Kerkaert and Huberman 2023; Sierra-Patev et al. 2023). For example, laccases and manganese peroxidases are the main genes encoding extracellular enzymes that degrade lignin in *L. edodes*, the genome of which does not contain lignin peroxidase (Chen et al. 2016). The mycelia of *L. edodes* first metabolize starch, followed by cellulose, hemicellulose, and lignin (Kobayashi et al. 2023a, b). Laccase is secreted first to degrade lignin before manganese peroxidase is utilized (Kobayashi et al. 2023a, b). Therefore, *L. edodes* mycelia showed different biological change laws during the mycelial colonization and browning stages under distinct nutritional and growth conditions (Fig. 1c).

Mycelial colonization stage

Mycelia surrounded by sufficient nutrients primarily perform primary metabolism to produce macromolecular precursors and free energy to support the synthesis of new cellular components required for mycelial growth (Fig. 1c; Ward and Thompson 2012; Song et al. 2023). As the most abundant monosaccharide in sawdust substrates and the preferred carbon source, glucose derived from cellulose and starch degradation can be transported into the mycelial cytoplasm and broken down into pyruvate by glycolysis (Fig. 1c, 2; Borkovich and Ebbole 2010). Pyruvate then enters the mitochondria and is converted to acetyl-CoA to provide carbon skeletons for the tricarboxylic acid (TCA) cycle, which is responsible for the oxidative phosphorylation system to drive energy (ATP) synthesis and also provides various carbon skeletons for anabolic processes (Fig. 2; Zhang and Fernie 2023). Glucose can also be oxidized to generate ribose 5-phosphate and nicotinamide adenine dinucleotide phosphate (NADPH) via the pentose phosphate pathway (PPP), which runs parallel to upper glycolysis but has a much lower flux than glycolysis under unstressed conditions (TeSlaa et al. 2023). As the most abundant monosaccharides in sawdust substrates after glucose, xylose and arabinose derived from hemicellulose degradation can be transported into the cytoplasm and converted to xylulose-5-phosphate to feed on PPP after the preferred utilization of glucose (Fig. 1c, 2; Seiboth and Metz 2011). Additionally, oligogalacturonides from pectin degradation can provide glyceraldehyde-3-phosphate for glycolysis and pyruvate for the TCA cycle, and β-ketoadipate derived from lignin can be converted into pyruvate, acetyl-CoA, and succinyl-CoA upon entering the TCA cycle (Fig. 1c, 2; Abbott and Boraston 2008; Del Cerro et al. 2021).

When the mycelia release extracellular enzymes to degrade carbon sources through exocytosis and carbon catabolism, the hyphal tip of the mycelia undergoes simultaneous polar growth, including the expansion of the surface of the cell membrane and cell wall, increased numbers of cytoplasmic inclusions and organelles, and mitosis of the nucleus (Song et al. 2023). The main components of *L. edodes* cell wall are polysaccharides, such as β-glucan and chitin, whose substrates are nucleotide diphosphate (UDP)-glucose and UDP-N-acetylglucosamine (UDP-N-GlcNAc), respectively (Gow et al. 2017; Brauer et al. 2023). The synthetic pathways for UDP-glucose and UDP-N-GlcNAc are derived from the glycolysis pathway (Fig. 1c, 2; Brauer et al. 2023). The main membrane components of the membrane trafficking system (i.e., the plasma membrane, endoplasmic reticulum, Golgi apparatus, endosomes, lysosomes, vacuoles, vesicles, and microvesicles), mitochondria, ribosomes, nucleus, and peroxisomes are lipids and proteins (More et al. 2020). Different functional membranes contain different amounts and types of lipids and proteins (Tan et al. 2008). Phospholipids, sphingolipids, and sterols (mainly ergosterol) are the most prevalent membrane lipids, whereas fatty acids are the building blocks for the synthesis of phospholipids and sphingolipids (Klug and Daum 2014). The synthesis of ergosterol and fatty acids in the cytoplasm uses acetyl-CoA as a substrate and NADPH as a cofactor (Fig. 1c, 2; Chandel 2021). Additionally, excess glucose and fatty acids can be stored in soluble carbohydrates (i.e., glycogen, mannitol and trehalose) in the cytoplasm and neutral lipid (i.e., triacylglycerols and sterol esters) in lipid droplets, respectively, when mycelial growth enters the stationary phase (Fig. 1c, 2; Ceccaroli et al. 2011; Wang 2015).

The process of protein biosynthesis consists of two stages. The first stage is the transcription of DNA into mRNA, where nucleotides are summoned to the nucleus to participate in the elongation of the mRNA chain (Alhalmi et al. 2020). The second stage is translation of mRNA into

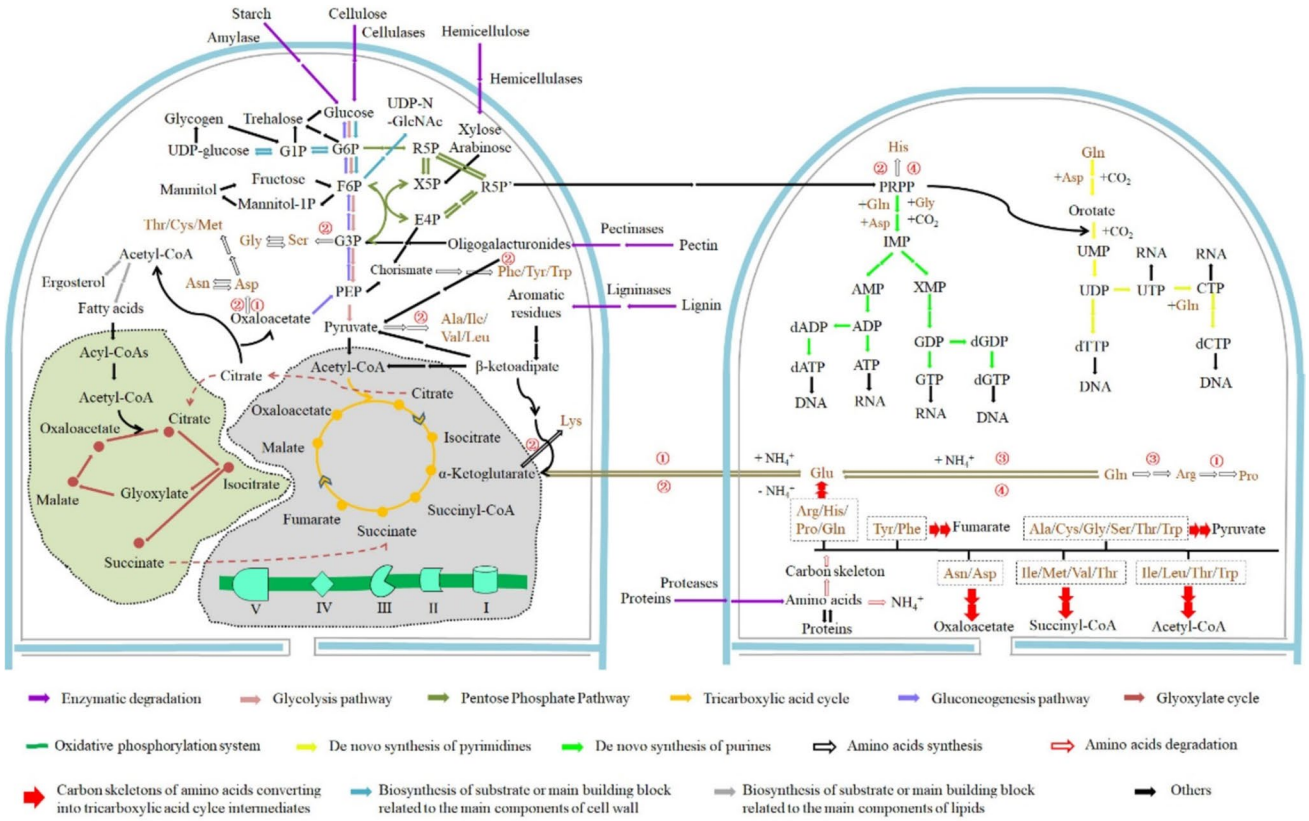

Fig. 2 Main metabolic network diagram of carbon (left) and nitrogen (right) sources in the vegetative growth stage of *L. edodes* mycelia. Metabolites: G6P, glucose-6-phosphate; G1P, glucose-1-phosphate; F6P, fructose-6-phosphate; G3P, glyceraldehyde-3-phosphate; PEP, phosphoenolpyruvate; R5P, ribulose-5-phosphate; R5P', ribose-5-phosphate; X5P, xylulose-5-phosphate; E4P, erythrose-4-phosphate; PRPP, phosphoribosyl pyrophosphate; IMP, inosine monophosphate; AMP, adenosine monophosphate; XMP, xanthine monophosphate; ADP, adenosine diphosphate; dADP, deoxyadenosine diphosphate; ATP, adenosine triphosphate; dATP, deoxyadenosine triphosphate; GDP, guanosine diphosphate; dGDP, deoxyguanosine diphosphate; GTP, guanosine triphosphate; dGTP, deoxyguanosine triphosphate; UMP, uridine monophosphate; UDP, uridine diphosphate; UTP, uridine triphosphate; CTP, cytidine triphosphate; dCTP, deoxycytidine triphosphate; dTTP, deoxythymidine triphosphate; DNA, deoxyribonucleic acid; RNA: ribonucleic acid. Amino acids: Ala, alanine; Arg, arginine; Asn, asparagine; Asp, aspartate; Cys, cysteine; Gln, glutamine; Glu, glutamate; Gly, glycine; His, histidine; Ile, isoleucine; Leu, leucine; Lys, lysine; Met, methionine; Phe, phenylalanine; Pro, proline; Ser, serine; Thr, threonine; Trp, tryptophan; Tyr, tyrosine; Val, valine. I-V: complexes of oxidative phosphorylation system. ①–④: transamination reactions between α-ketoglutarate and glutamate and between glutamate and glutamine. Dashed lines indicate that metabolites move through different sections of the cell. Green and gray backgrounds indicate that reaction takes place in the lysosome and mitochondria, respectively

proteins, where amino acids are required to participate in the extension of polypeptide chains (Alhalmi et al. 2020). There are two types of nucleotides: pyrimidines (CTP, UTP, dTTP, and dCTP) and purines (GTP, ATP, dGTP, and dATP), which can be used for DNA or RNA synthesis (Fig. 1c, 2; Mullen and Singh 2023). The de novo synthesis of pyrimidines and purines involves a complex series of steps that transform amino acids (mainly glutamine and aspartate) and phosphoribosyl pyrophosphate (PRPP) into uridine monophosphate and inosine monophosphate, respectively (Fig. 2; Chen et al. 2023; Mullen and Singh 2023). PRPP is an activated form of ribose-5-phosphate derived from PPP (Fig. 2; Hove-Jensen et al. 2016). Amino acids for protein synthesis can be synthesized from intermediates of glycolysis and the TCA cycle mainly via a central core pathway of nitrogen metabolism involving transamination reactions between α-ketoglutarate and glutamate and between glutamate and glutamine (Fig. 2; Bianchi et al. 2019). Therefore, the mycelia of *L. edodes* can grow normally in wild wood log without additional nitrogen-rich substrates. Proteins from wheat bran added to sawdust substrates can be degraded into amino acids to replenish the carbon skeleton of the TCA cycle and provide the preferred nitrogen sources (i.e., NH_4^+, glutamine, and glutamate) (Fig. 2; Chandel 2021).

Changes in the physical and chemical indices of *L. edodes* mycelia in the mycelial colonization stage can further verify the internal metabolic changes. With the continuous increase of mycelial biomass, the content of *L. edodes* polysaccharide including β-glucans, also increases, while the contents of cellulose, hemicellulose, and lignin continue to decrease

(Sánchez and Montoya 2020). The changes in these five types of components are related to the processes of cell wall remodeling and extracellular enzyme release for cellulose, hemicellulose, and lignin degradation, which are mediated by exocytosis during apical growth (Song et al. 2023). Acidification of sawdust substrates to a pH of 3.5 to 4.0 is essential for mycelial growth of *L. edodes* and enhances lignin degradation, as most laccases and manganese peroxidases require acidic conditions for optimal activity (Li et al. 2022; Kijpornyongpan et al. 2022). Many primary carbon metabolic pathways, especially the TCA cycle, can produce organic acids, such as citrate, succinate, malate, and oxalate (Chroumpi et al. 2020). Thus, the pH of *L. edodes* sawdust substrates decreases steadily throughout the colonization process (Philippoussis et al. 2003). In addition, to clarify the metabolic rule of *L. edodes* mycelial colonization period, some measures are often adopted in production to improve the formula of the sawdust substrate or shorten the colonization time. For example, supplementation with 1–3% gypsum ($CaSO_4 \cdot H_2O$) can significantly increase biological efficiencies and yield by relieving the toxicity of oxalate and facilitating the acidification of sawdust substrate (Li et al. 2022). A one-time puncturing of the plastic bags and pine turning during the *L. edodes* colonization process are better aerobic techniques to increase the oxygen supply, promote mycelial growth, and shorten colonization times (Wang et al. 2019).

Browning stages

With the mycelia completely colonizing the entire sawdust substrate, many physicochemical and nutritional components of the substrate have changed to limit mycelial growth, such as decreases in pH and oxygen content and depletion of preferred carbon and nitrogen sources. These limiting factors can trigger specific stress responses that are integrated at the molecular level and control the biosynthesis and differentiation of specific secondary metabolites (Fig. 1c; Martín et al. 2011; Tudzynski 2014; Yu et al. 2023). Fungal secondary metabolites are small molecules that mainly include three chemical categories (polyketides, terpenes, and non-ribosomal peptides) and hybrid molecules (polyketide-terpene, non-ribosomal peptide-polyketides, and polyketide-fatty acid) (Keller 2019). Core polyketide compounds are condensed from simple precursors, such as acetyl-CoA and malonyl-CoA, catalyzed by the core polyketide synthase enzyme (Stroe et al. 2024). Terpenes are molecules derived from isopentenyl diphosphate and dimethylallyl diphosphate, both of which are synthesized via the mevalonate pathway, starting with acetyl-CoA (González-Hernández et al. 2023). Non-ribosomal peptide synthesis occurs via a thiotemplate mechanism in peptide synthetases in the order of the addition of each unusual amino acid, including non-proteinogenic or modified amino acids (Moffitt and Neilan 2000). The loss or overproduction of specific secondary metabolites at the right time can alter fungal development (hyphal differentiation, spore formation, and pigment generation) and confer evolutionary advantages (survival and competitive advantage) (Keller 2019; Yu et al. 2023).

Light, especially ultraviolet (UV) radiation, is one of the greatest pressures on *L. edodes* mycelial growth and survival during the browning stage. The first line of the mycelial defense mechanism against UV radiation is the same as that in the human skin by accumulating melanin (an epidermal polyketide-derived pigment) in the surface tissue to block UV radiation and harmlessly dissipate as harmless heat (Fig. 1c; Mohania et al. 2017; Stroe et al. 2024). The surface mycelia of synthetic substrate logs can form a brown film via melanin accumulation in the cell wall, intracellular spaces, and intercellular spaces (Yan et al. 2020). With the increasing irradiation time, the area of the brown film continued to expand and the color of the parts already containing melanin appeared to darken (Song et al. 2021). According to precursor substances of synthetic pathways, fungal melanin can be classified into 1,8-dihydroxynaphthalene (DHN) melanin, pyomelanin, eumelanin, phenomelanin, 4-glutaminylhydroxybenzene (GHB) melanin, 4-aminophenol (PAP) melanin, and so on (Liu et al. 2022). Based on genomic annotation, *L. edodes* lacks genes related to the biosynthesis pathways of DHN-melanin and pyomelanin, and its own genes related to those of eumelanin, pheomelanin, GHB melanin, PAP melanin, and catechol melanin (Du et al. 2023). The biosynthetic pathways of eumelanin and phenomelanin use tyrosine as the precursor and tyrosinase as the key enzyme, whereas those of GHB melanin, PAP melanin, and catechol melanin use chorismate as the precursor and tyrosinase as the key enzyme (Du et al. 2023).

Reactive oxygen species (ROS) are a class of unstable chemicals that mainly include hydroxyl radicals (·OH), superoxide anions ($O_2^{\cdot -}$), singlet oxygen ($^1O_2$), and hydrogen peroxide (H_2O_2) (Liu et al. 2023). Intracellular ROS are mainly produced through two mechanisms (Aranda-Rivera et al. 2022; Liu et al. 2023): as by-production of mitochondrial electron transport chain that electrons leak prematurely from complexes I, II, and III to mediate the one-electron reduction of oxygen to $O_2^{\cdot -}$, as by-products of several cellular enzymes, such as NADPH oxidases, xanthine oxidoreductase, and lipoxygenases. For example, some NADPH oxidases can accelerate the reaction of NADPH with molecular oxygen to produce $O_2^{\cdot -}$ (Liu et al. 2023). Guan et al. (2022) showed that H_2O_2 is the main ROS in the browning stages *L. edodes*. H_2O_2 is generated from $O_2^{\cdot -}$ and can subsequently be converted to other ROS (Liu et al. 2023). To maintain homeostasis, ROS also can be eliminated through an oxidative defense system that comprise endogenous antioxidant enzymes (i.e., superoxide dismutase, catalase, and glutathione peroxidase) and low-molecular-weight scavengers

(i.e., vitamins, coenzyme Q, zinc, and melatonin) (Liu et al. 2023). Under normal physiological conditions, ROS are maintained at relatively low levels by balancing between the production and elimination, and play central roles as second messengers in regulating multiple signaling pathways, such as nuclear factor-kappa B, mitogen-activated protein kinase, and nuclear factor erythroid 2-related factor 2 (Liu et al. 2023). However, UV radiation that escapes brown film absorption can generate ROS through various mechanisms that disrupt the balance of reduction-oxidation (redox), induce oxidative stress, oxidize cellular components (i.e., proteins, lipids, and nucleic acids), and trigger cell death (i.e., autophagy) (Galganska et al. 2010; Liu et al. 2023). Therefore, the metabolic flux of the oxidative defense system should be upregulated to balance redox reactions during the browning stage.

Faced with internal and external stresses during the browning stage, *L. edodes* mycelia activate various mechanisms to maintain nutrient and energy homeostasis for survival. One mechanism is to expand the source of glucose by quickly degrading glycogen and triggering gluconeogenesis, whereby glucose is formed from noncarbohydrate carbon precursors, including pyruvate (Fig. 1c, 2; Judge and Dodd 2020). The second mechanism is to change the main glucose consumption pathway from glycolysis to the PPP, which ensures that sufficient amounts of NADPH are produced for subsequent events, such as maintaining the redox balance, as electron donors for endogenous antioxidant enzymes (Fig. 1c; Oka et al. 2012; Judge and Dodd 2020; TeSlaa et al. 2023). The third mechanism is to trigger the stress-induced catabolic pathway of autophagy in lysosomes to break down damaged or non-essential cellular structures and recycle the resulting metabolites for core biosynthetic processes or energy production (Fig. 1c; He 2022). Proteins, nucleic acids, carbohydrates, and lipids can be degraded into their constituent amino acids, nucleotides, glucose, and fatty acids, respectively, during autophagic metabolism (He 2022). In addition, glycogen degradation, organelle turnover, and selective degradation of ribosomes, including rRNA and mRNA, are mediated by autophagy (He 2022). The final mechanism is to promote a shift from carbohydrate to lipid metabolism for energy generation (Fig. 1c). The glyoxylate cycle, which uses acetyl-CoA to generate oxaloacetate in peroxisomes, has emerged as an alternative carbon metabolic pathway when glucose availability is limited (Kijpornyongpan et al. 2022). This cycle can provide intermediates and NADH for the TCA cycle to generate ATP and can also provide precursors for gluconeogenesis (Fig. 2; Kijpornyongpan et al. 2022). The acetyl-CoA is mainly generated by β-oxidation of fatty acids, which are produced from degradation of neutral lipid (i.e., triacylglycerols and sterol esters) in lipid droplets and cellular structural lipids (Fig. 2; Huang et al. 2023).

Exploration of the molecular mechanism of brown film formation has always been a hot topic in the study of *L. edodes*. Many studies relying on comparative omics techniques can further elucidate the main metabolic process of mycelia during the browning stage. Transcriptomic analysis revealed that light reception, light signal transduction pathways, melanogenesis, cell wall degradation, pentose and glucuronic acid conversion, and starch and sucrose metabolism are important for light-induced brown film formation (Tang et al. 2013; Yoo et al. 2019; Huang et al. 2020). Based on proteomic analyses, small-molecule metabolic processes, responses to oxidative stress, oxidation-reduction processes, light signal transduction, cell wall degradation, and melanogenesis are associated with brown film formation (Tang et al. 2016; Song et al. 2020). Based on a metabolomic analysis, Tang et al. (2022) found that oxidative stress and autophagy are important processes in brown film formation. Growers usually browse *L. edodes* using two different methods: browning in the bag and browning outside the bag (Shen et al. 2008). Compared with browning in the bag, browning outside the bag requires a shorter browning time but also requires increased management input and special management techniques, such as control of carbon dioxide levels, humidity, and watering log surfaces (Shen et al. 2008). In China, browning in bags with less handling and reduced management input is more popular with farmers, and plastic bags are punctured once before the beginning of the browning stage to shorten browning time (Shen et al. 2008).

Reproductive growth

Fruiting body induction

Many physiological and environmental factors, individually or in combination, influence fruiting body induction in basidiomycetes (Sakamoto 2018). Physiological factors include nutrient starvation (lower nitrogen and carbon concentrations) and chemical compounds (i.e., cAMP, cerebrosides, saponins, lectin, lipid phosphate, and ergosterol) (Fig. 1c; Ohga et al. 2000; Lu et al. 2016; Sakamoto 2018). The term used for production is called mycelial physiological maturity, which means that these physiological factors can trigger fruiting body formation after reaching specific values. However, what these values are, and whether they work together or individually, is unknown. In the production of *L. edodes*, the mycelial physiological maturity of synthetic logs is generally determined by the number of culturing days from inoculation (unique to each cultivar) and the surface characteristics of the synthetic logs, such as reddish-brown brown film, tumor-shaped nodules or softness to touch (Huang 1994; Yu et al. 2022b). The environmental factors include light, water, temperature, vibrations,

electrical stimulation of high-voltage, and others (Fig. 1c; Takaki et al. 2014; Sakamoto 2018; Kobayashi et al. 2023a, b). With the growing scale of *L. edodes* cultivation, many companies specializing in the preparation and cultivation of synthetic logs and sales of synthetic logs with physiologically mature mycelia to other regions and countries to form fruiting bodies have emerged in China. To lengthen the transportation time, these logs are mostly stored at low temperatures or frozen. In this case, the low temperature and vibrations during transportation should be the crucial environmental factors for *L. edodes* fruiting body induction. The findings of Song et al. (2021) provide a good explanation for the effects of physiological and environmental factors on the induction of *L. edodes* fruiting bodies. When the culturing time is long enough, fruiting bodies can be formed without environmental stimulation. This stimulation shortens the fruiting time and improves the agronomic characteristics of fruiting bodies (i.e., number and size of fruiting bodies).

Fruiting body development

As the most complex three-dimensional structure produced by fungi for efficient spore dispersal, fruiting bodies follow a genetically encoded developmental program that orchestrates growth, tissue differentiation, and sexual sporulation (Nagy et al. 2023). Developmental events that occur in *L. edodes* fruiting bodies are far fewer than those of *Coprinopsis cinerea*, *Schizophyllum commune* and *Agaricus bisporu*s. However, this does not prevent us from predicting those of *L. edodes* from their basic common developmental events (Kües and Liu 2000; Baars et al. 2020; Nagy et al. 2023). First, hyphal knots (primary nodules) with interacting mycelia form on sexually competent mycelia as the reprogramming of hyphal branching patterns, which is triggered by physiological and environmental factors (Fig. 1c; Kües and Liu 2000; Nagy et al. 2023). Gradually, branches in the hyphal knots aggregate to form a fluffy spherical mycelial association, called an aggregate or second nodule, and then the aggregates undergo tissue differentiation to form primordia, which contain all the different tissues present in the mature fruiting body (Kües and Liu 2000). Different fungal species have different tissues, including the veil, pileus, gills, hymenium, stipe, and basal plectenchyma (Virágh et al. 2022). The development of mature fruiting bodies from primordia is a tightly regulated and irreversible process, such as stipe elongation, which starts immediately after meiosis takes place in the hymenium, after which basidiospore production, maturation, and cap expansion follow a tightly choreographed chronology (Nagy et al. 2023).

The molecular mechanism of *L. edodes* fruiting body development has been the subject of intense research. However, owing the relative difficulty of testing hypotheses through genetic manipulation, many results remain in the prediction stage, relying on comparative omics techniques (Nagy et al. 2023). Moreover, because of the different samples and research purposes, the results have been variable. This phenomenon is commonly observed in Agaricomycetes. Nagy et al. (2023) summarized the most complete description of molecular processes in the fruiting body development of Agaricomycetes, based on literature data, conserved expression patterns, and functional annotations. Briefly, fruiting body development in Agaricomycetes includes three phases: early events (primordium formation and cell proliferation), cell expansion, and late events (sexual processes and sporogenesis) (Fig. 1c; Nagy et al. 2023). Early events are also termed the proliferative phase of development, and the upregulated genes are mainly related to mitotic cell division and remodeling of fruiting body-specific plasma membranes and cell walls. At the stage of growth by cell expansion, cell proliferation is largely complete, and the upregulated genes are mainly involved in membrane biosynthesis, metabolic genes of acetyl-CoA synthesis, cell wall remodeling enzymes, and some storage carbohydrate (trehalose, glycogen, and mannitol) metabolic genes, which are upregulated in the gills and provide storage materials for spores rather than turgor manipulation. During late events, the upregulated genes were mainly related to meiosis and gills storage carbohydrate metabolism, whose metabolites (trehalose, glycogen, and mannitol) can be packaged into spores.

In the production of *L. edodes*, the formation of primordia usually occurs under the bark as logs, and the development from primordia to mature fruiting bodies occurs on the surface of the bark and can be immediately affected by many environmental factors (Kües and Liu 2000; Moore et al. 2008; Sakamoto 2018). In general, fruiting body maturation requires longer exposure to high energy, and light affects pileus formation, pileus color, stipe elongation, and its direction (positive phototropism). A high concentration of carbon dioxide suppresses pileus formation and spore formation but promotes stipe elongation. High humidity (90–95%) is favorable for fruiting body maturation. Optimum temperatures for fruiting body formation are generally lower than those most favorable for mycelial growth. A pH of 4 is optimal for fruiting body formation in *L. edodes*. Additionally, various soluble carbohydrates (i.e., glycogen, trehalose, and mannitol) and water that mycelia accumulate before fruiting are critical for the development of fruiting bodies (Herman and Bleichrodt 2022). Trehalose is synthesized from glycogen in the mycelia, transported to the fruiting body, and rapidly converted to glucose and glucose-1-phosphate to supply the main carbohydrate substrates for development (Fig. 2; Kües and Liu 2000; Kitamoto et al. 2001; Patyshakuliyeva et al. 2013). Mannitol is synthesized from fructose in mycelia using NADPH as a cofactor (Patyshakuliyeva et al. 2013). It is transported to the fruiting

body as an osmoregulatory compound and facilitates the continuous influx of water from the compost to the fruiting body (Fig. 2; Kües and Liu 2000; Kitamoto et al. 2001; Patyshakuliyeva et al. 2013). Water can supply turgor to fruiting bodies, such as stipe elongation and pileus expansion, and it accounts for more than 90% of the fruiting body structure (Herman and Bleichrodt 2022). Based on these principles, growers usually reduce the number of young fruiting bodies and adjust easily regulated factors (i.e., light, water, temperature, and carbon dioxide concentration) to effectively utilize the accumulated carbohydrates and obtain fruiting bodies with good shapes and high yields. When the edge of the pileus is still in-rolled or when the pileus is only partly extended (60–70%), *L. edodes* fruiting bodies can be harvested and sold fresh or dry (Chen 2001).

Prospect

The original intentions of writing this review were to comprehensively analyze the relationship between *L. edodes* cultivation methods and biology and to construct a panoramic map of biological penetration into various stages of *L. edodes*. These aims can help understand the current situation and predict the direction of development of *L. edodes* cultivation. However, this plan proved difficult; although there are many articles on the biology of cultivation methods for *L. edodes*, most of them focus on several hot topics (i.e., cultivar identification and light-induced brown film formation), with a lack of focus on the biological development of cultivation methods. Additionally, because of the influence of the sample, substrate formula, cultivation measures, sampling time, and other factors, the results of different articles addressing the same topic have been quite different, especially for some volatile quantitative indicators, such as extracellular enzyme activity, physical and chemical indicators, gene expression, proteins, and metabolites. Therefore, this review can only begin to build a preliminary framework with the exploration of the universal biological law, or even with the help of other edible fungi (i.e., fruiting body development) or humans (i.e., some measures in response to harmful light and starvation) (Fig. 1c). Further research should be refined and expanded on this basis. For example, continued examination of microscopic biological contents, such as signal transduction, transcriptional genes, and epigenetics, will be valuable, as will supplementation with other biological cultivation processes, such as the two-to-four times process of vegetative growth and reproductive development after the first harvesting of fruiting bodies.

Based on the preliminary framework of the relationship between *L. edodes* cultivation methods and biology presented in this review, the biological research hotspots related to cultivar selection, vegetative growth, and reproductive development can be easily inferred. For example, the similarities and differences in phenotype and cultivation characteristics among different wild populations or subgroups of *L. edodes* can be revealed. Special goals include the development of easy-to-operate molecular identification techniques that can clearly distinguish the genetic information of two sets of nuclear and one set of mitochondrial genomes in each cultivar, overcoming the technical difficulties of genetic transformation and deciphering the relationship between *L. edodes* genome and its growth and development, deducing the metabolic rule and operation mechanism of preferred carbon and nitrogen nutrients, clarifying the mycelial physiological signals that induce fruiting body formation, and identifying signaling factors that regulate the step-by-step development of fruiting bodies. In addition, it is clear that the genetic background of the two sets of nuclear and one set of mitochondrial genomes of the cultivar is key in affecting the vegetative growth and reproductive development of *L. edodes* (Song et al. 2023). Therefore, we predict that the next milestone in *L. edodes* cultivation may be related to cultivar breeding after the shock method, pure culture spawn, and synthetic sawdust log methods. This may be due to the huge cultivation technology reforms brought about by genetic background changes or growth characteristic breakthroughs of cultivars.

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Data availability No additional data are available.

Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

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