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REVIEW ARTICLE

Value-added biotransformation of agricultural byproducts by cellulolytic fungi: a review

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ABSTRACT

Agricultural byproducts generally contain abundant bioactive compounds (e.g., cellulose/hemicellulose, phenolic compounds (PCs), and dietary fibers (DFs)), but most of them are neglected and underutilized. Owing to the complicated and rigid structures of agricultural byproducts, a considerable amount of bioactive compounds are entrapped in the polymer matrix, impeding their further development and utilization. In recent years, the prominent performance of cellulolytic fungi to grow and degrade agricultural byproducts has been applied to achieve efficient biotransformation of byproducts to high-value compounds, which is a green and sustainable strategy for the reutilization of agricultural byproducts. This review comprehensively summarizes recent progress in the value-added biotransformation of agricultural byproducts by cellulolytic fungi, including (1) direct utilization of agricultural byproducts for biochemicals and bioethanol production via a consolidated bioprocessing, (2) recovery and biotransformation of bounded PCs from agricultural byproducts for higher bioactive properties, as well as (3) modification and conversion of insoluble DF from agricultural byproducts to produce functional soluble DF. The functional enzymes, potential mechanisms, and metabolic pathways involved are emphasized. Moreover, promising advantages and current bottlenecks using cellulolytic fungi have also been elucidated, shedding further perspectives for sustainable and efficient reutilization of agricultural byproducts by cellulolytic fungi.

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Cellulolytic fungi; agricultural byproducts; consolidated bioprocessing; phenolic compounds; dietary fiber; biochemicals

Introduction

The development of the agri-food industry and increasing demand for high-value food markets annually generates varieties of byproducts including plant stems, leaves as well as fruit pomaces, etc. These agricultural byproducts usually account for a large proportion of fresh products [1], and extensively contain several potential bioactive compounds, such as cellulosic polysaccharides, phenolic compounds (PCs), and dietary fibers (DFs) [2]. The cellulosic composition of plants, especially those straws and stovers, are promising sources of glucose and pentose, whose hydrolysates are promising carbon sources for microbes to synthesize other value-added bioproducts [3]. Besides, the plant-based natural chemicals, such as PCs with brilliant anti-cancer, and anti-oxidation ability are widely distributed in byproducts with ranged titers and functions according to their compositions [4]. Moreover, some functional polysaccharides, such as DF, which are native bioactive compounds with potential health benefits, are extensively presented in agricultural byproducts [5]. Despite the abundant bioactive components presented in agricultural byproducts, these byproducts are mostly underutilized through: landfilling, discarding, using for animal feed, or burning, which have lost most of their value and even threaten the environment. It is worth mentioning that these agricultural byproducts are highly polymeric, with rigid and complex structures formed by cellulose, hemicellulose, and other components. The bioactive potential compounds inside byproducts are largely trapped or linked to the polymer matrix, hindering their extraction separation and further reutilization (Figure 1).

Different strategies, including physical, chemical, and biological methods, have been applied for

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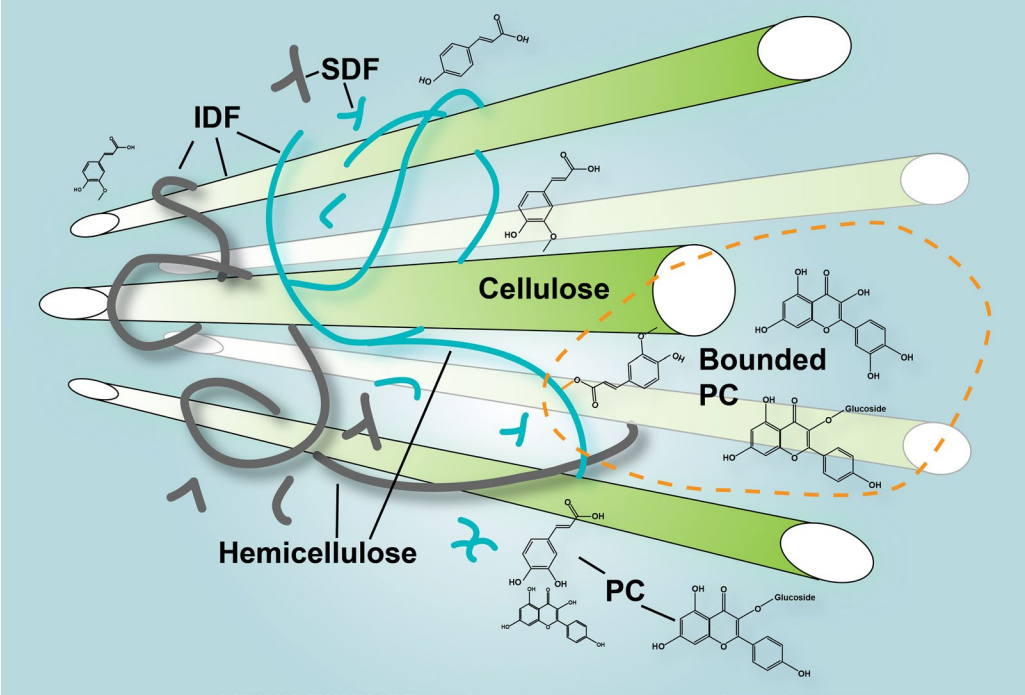

Figure 1. Overview of the structures in agricultural byproducts. The agricultural byproducts are highly polymeric, with rigid and complex structures formed by cellulose, hemicellulose, and other components. Cellulose is sheet-like spread with the crystalline structure with hemicellulose surrounded. Insoluble dietary fiber (IDF) mainly represents cellulose and hemicellulose, accounting for a large proportion of agricultural byproducts. While soluble dietary fiber (SDF) refers to those fragments with highly branched structures, only accounts for a small part of agricultural byproducts. Moreover, phenolic compounds (PCs) are extensively presented, and many of them are presented with their bounded form, blocked, intertwined, or linked in the rigid structures by cellulose and hemicellulose.

recovery of functional components from agricultural byproducts with varied efficiency. Among that, biological strategies are considered green approaches with high efficiency and also environmental-friendly [6], which is generally accepted for food and feed industries. However, the high cost of enzyme production is still a bottleneck for industrial application. To date, the microbial fermentation-based strategy has been applied to efficiently utilize agricultural byproducts and produce value-added compounds [7,8]. Microbes, especially cellulolytic fungi, are capable of secreting hydrolyzing enzymes, including cellulase and hemicellulose, to degrade and utilize agricultural byproducts, then releasing and producing bioactive compounds. Commonly used cellulolytic fungi are *Aspergillus spp*, and *Trichoderma spp*, etc., some of which have been widely used as starters in food and wine fermentation, and are accepted as generally recognized as safe (GRAS) strains in food industries [9,10]. These fungi could robustly grow on agricultural byproducts, cleave the link between polymeric polysaccharides to loosen the compact structures, and release entrapped bioactive compounds [6]. Of note, bioactive compounds recovered after fungi treatment usually exhibit higher bioactive characteristics, probably owing to modified structures and varied compositions [5, 11], lighting the prominent performance of cellulolytic fungi in this process. Moreover, the breakdown of cellulosic components to mono/di-saccharides also enables their further metabolism to other bioproducts [12], thus making these cellulolytic fungi promising candidates for economical one-step synthesis of bioproducts direct from agricultural byproducts.

Considering the brilliant performance of cellulolytic fungi in the fermentation of agricultural byproducts, increasingly attempts have been made to improve the efficiency of cellulolytic fungi in the biotransformation of agricultural byproducts either by: deciphering the key factors during fermentation [13], improving the cellulase production [14], regulating metabolic flux [15], or isolating novel strains with excellent cellulase output [16]. Although a few achievements have been made in the efficient biotransformation of agricultural byproducts to bioactive compounds, some bottlenecks still exist owing to the insufficient understanding of the mechanism of bioactive compound transformation, as well as the poorly explored genetic background of cellulolytic fungi. Thus, it is difficult to make further

improvements to realize efficient agricultural byproducts biotransformation. Moreover, current reviews mainly focused on the effect of different microbe fermentation either on: consolidated bioprocessing (CBP) [17], bio-based PC extraction [1], or DF modification [5] individually. However, the critical function of cellulolytic fungi in biotransformation has not been emphasized. This review aims to summarize recent advances of cellulolytic fungi in value-added biotransformation from agricultural byproducts, including: consolidated synthesis of bioproducts, PC extraction, and DF modification. The function and mechanism of cellulolytic fungi in the biotransformation have been discussed based on current studies and the key enzymes, as well as their cooperative networks, are emphasized, giving new clues for applying and engineering cellulolytic fungi for efficient utilization of agricultural byproducts.

Direct utilization of agricultural byproducts for biochemicals and bioethanol production

Agricultural byproducts especially cellulosic byproducts, including rice straw, corn stover, and corncob, are intractable problems due to their large proportions, rigid structures, and difficulty in disposal. These lignocellulosic byproducts are mainly composed of cellulose (40–50%), hemicellulose (20–30%), and lignin (10–25%) [18]. The hydrolysates of agricultural byproducts rich in glucose and xylose have been successfully developed for biochemicals and bioethanol production using different microorganisms [18–21]. However, the traditional biorefinery process needs continuous and individual steps such as cellulase production, hydrolysis, and fermentation, which are labor-intensive and costly. Recently, a novel strategy named CBP combining the cellulase production, enzyme hydrolysis, and fermentation in one process, has gained increasingly attention owing to cost-effectiveness [22]. Successive efforts have been made to engineer bacteria and yeast to utilize cellulosic substrates for direct biochemicals and biofuels production from cellulosic substrate, but their ability to utilize the real lignocellulosic byproducts is still challenging [3, 8, 23,24]. Cellulolytic fungi could robustly grow cellulosic agricultural byproducts, and could also produce many metabolites of high value for the food and pharmacy industry [25], making these fungi promising candidates for direct production of biochemicals and biofuels from agricultural byproducts.

In this section, we mainly summarize recent advances of cellulolytic fungi on biochemicals and bioethanol production directly from agricultural byproducts. The genes involved in biochemicals and bioethanol synthesis are illustrated, and the strategies used for improving synthesis efficiency are also emphasized. Moreover, we also review and discuss the advantages and bottlenecks of an alternative strategy of CBP by using a co-culture consortium with cellulolytic fungi. For extensive studies of CBP by other microorganisms (e.g., engineered yeasts, cellulosic bacteria), we suggest recent reviews by Singhania et al. [17] and Re and Mazzoli [3].

Applying cellulolytic fungi for biochemicals and bioethanol synthesis from agricultural byproducts

Some cellulolytic fungi, such as *Aspergillus* spp., are good producers of metabolites as valuable biochemicals. However, the direct synthesis of these metabolites from lignocellulosic agricultural byproducts has hardly been reported by way of a native fungus. Generally, the synthesis of metabolites by fungi is tightly regulated in native strains, such as low pH for citric acid production in *Aspergillus niger* [26] or high glucose concentration for itaconic acid in *Aspergillus terreus* [27]. While fermentation with cellulosic substrates is a glucose-limited process, which is not suitable for biochemical synthesis, besides, in some cases, the expression of gene clusters for metabolite synthesis is mostly repressed or silent [20], making the direct synthesis of biochemicals from agricultural byproducts difficult to realize. Ethanol is another promising end-product from lignocellulosic agricultural byproducts. Except for the brewing yeast *Saccharomyces cerevisiae*, many cellulolytic fungi are capable of ethanol fermentation from hexose, pentose, and lignocellulosic substrates [28]. However, their ethanol fermentation ability is much poorer than that of *S. cerevisiae*, probably because of the less efficient native ethanol synthesis pathway.

In the past five years, genetic engineering of cellulolytic fungi for biochemical and bioethanol production from lignocellulosic substrate gained increasing attention which could benefit cost-effective biorefinery process (Figure 2, Table 1). A cis-aconitic acid decarboxylase CAD1 from *A. terreus* heterologously expressed in *Neurospora crassa* achieves direct itaconic acid synthesis from Avicel, corn stover, and switchgrass, with a titer of 20.4, 10.4, and 8.6 mg/L, respectively [29]. Construction of a β-carotene synthesis pathway in *Trichoderma reesei* through overexpressing a phytoene dehydrogenase *carB* and a phytoene synthase/lycopene cyclase *carRP* from *Mucor circinelloides* enables efficient β-carotene production, further metabolic engineering achieved a 286.63 mg/L β-carotene production with Avicel and wheat bran as carbon sources [32]. Efficient malic acid production in an industrial thermal cellulolytic fungus *Myceliophthora thermophila* has been achieved by introducing a malic acid exporter

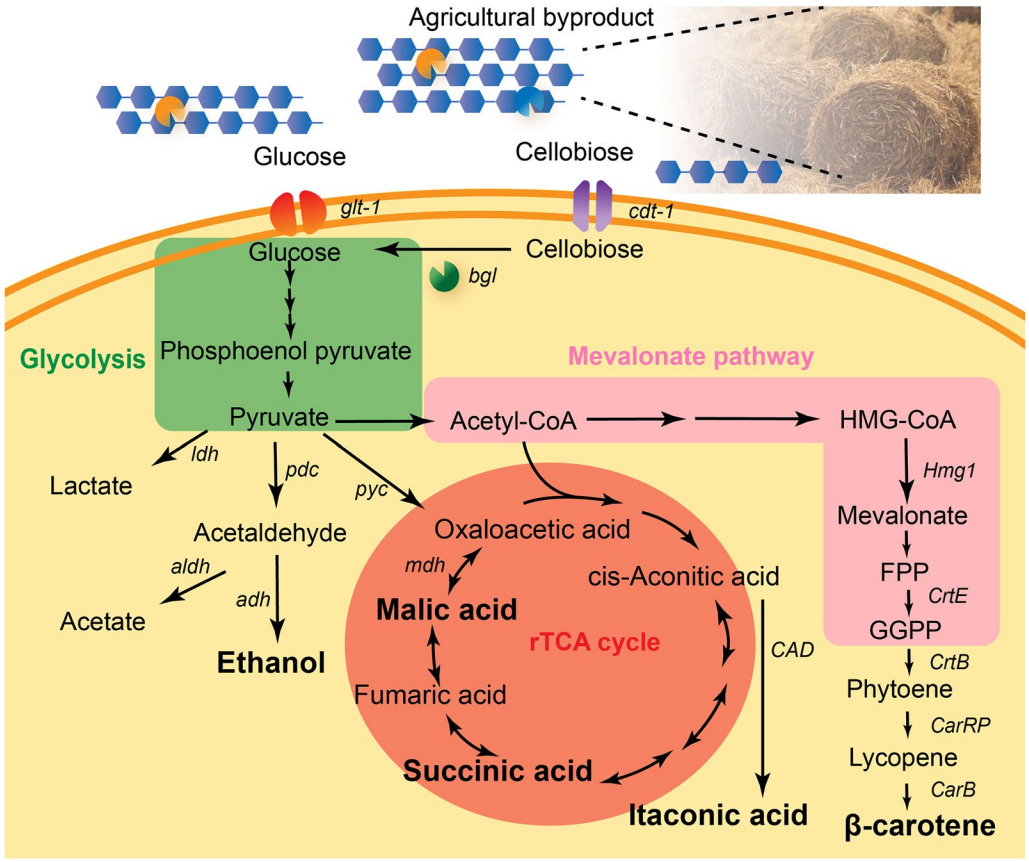

Figure 2. The diagram of the synthetic pathway of different biochemicals mentioned in this study through fungal CBP. The synthesis of biochemicals from agricultural byproducts is started from the degradation of cellulosic agricultural byproducts. The released glucose and cellobiose are transported intracellularly and are metabolized through glycolysis, rTCA cycle as well as the mevalonate pathway. The biochemicals synthesized are emphasized as bold, and the main genes participated in the synthesis are also annotated. Glt-1: glucose transporter; cdt-1: cellobiose transporter; bgl: intracellular β-glucosidases; ldh: lactate dehydrogenase; pdc: native pyruvate decarboxylase; pyc: pyruvate carboxylase; aldh: aldehyde dehydrogenase; adh1: alcohol dehydrogenases; mdh: malate dehydrogenase; CAD1: cis-aconitic acid decarboxylase; carRP: phytoene synthase/lycopene cyclase; carB: phytoene dehydrogenase; hmg1: hydroxymethylglutaryl-CoA reductase; crtE: geranylgeranyl diphosphate synthase; FPP: farnesyl diphosphate; GGPP: geranylgeranyl diphosphate.

and pyruvate carboxylase from *A. oryzae*. The resultant strain JG207 reached a maximum titer of 181 g/L malic acid from Avicel and 105 g/L from corncob in a fed-batch system [30]. Systematical engineering of malic acid synthesis has also been applied in *M. thermophila*, reaching a maximum yield of 1.11 g/g from 75 g/L Avicel, and 0.53 g/g plant biomass from 75 g/L raw corncob [30]. Improved ethanol production has been achieved by integrating an alcohol dehydrogenase Adh1 from *S. cerevisiae* [7], following stepwise metabolic engineering finally realized a maximum bioethanol yield of 52.8 g/L on Avicel and 39.8 g/L on raw corncob under fed-batch model [15].

Genetic strategies for enhancing biochemicals and bioethanol synthesis from cellulosic substrate

Generally, in the CBP process, cellulolytic fungi must coordinate cellulose degradation and biochemicals/bioethanol synthesis. A good correlation between cellulase production and malic acid synthesis has been observed in engineered *M. thermophila* [30]. Systematical engineering of the ethanol synthesis by: optimizing the synthetic pathway, enhancing the glycolytic rate, inhibiting mitochondrial NADH shuttles, and knocking out the ethanol consumption pathway, resulted in a nearly 280-fold increase of ethanol yield on Avicel in strain YL913. Meanwhile, a 8.8-fold improvement in cellulase production is also observed in strain YL913 [15], indicating that improved cellulase expression is required to meet the nutrient requirement for the efficient production of biochemicals. However, enhancing the cellulase production by overexpressing the cellulase activator Clr-2 did not improve the malic acid production from cellulosic substrates [30], suggesting that a subtle metabolic flux is presented in fungi to drive the biochemicals and bioethanol synthesis.

Table 1. Recent advances of CBP for biochemicals and bioethanol production by cellulolytic fungi.

Fungi	Genetic modification	Substrates	Products	Yield	Productivity	Ref.
N. crassa	OE:CAD1	Avicel	Itaconic acid	20.4 mg/L	–	[29]
		Corn stover		10.4 mg/L		
		Switchgrass		8.6 mg/L		
M. thermophila	OE: Aomae, Aopyc	75 g/L cellulose	Malic acid and succinic acid	65.4 g/L malic acid and 7.2 g/L succinic acid	0.97 g/g	[30]
		75 g/L xylan		48.7 g/L malic acid and 12.1 g/L succinic acid	0.81 g/g	
		Avicel fed-batch		181 g/L malic acid and 19.7 g/L succinic acid	1.1 g/g	
		Corncob fed-batch		105 g/L malic acid and 5.4 g/L succinic acid	0.4 g/g plant biomass	
	OE: Aomae, Aopyc, *glt-1, ppc1, mdh, bicA,* ca. Del: *pdc, ldh, pck*	75 g/L Avicel	Malic acid	83.3 g/L	1.11 g/g	
			Succinic acid	15.4 g/L	1.32 g/g	
M. thermophila	OE: Aomae, Aopyc, *Ctcpp, cdt-1*; Del: *bgl2, bgl3*	75 g/L Avicel	Malic acid	77.4 g/L	1.03 g/g	[31]
M. thermophila	OE: Aomae, Aopyc, *cbbM, prk, gal2M*; Del: *pdc, ldh, pck*	75 g/L raw corncob	Malic acid	40 g/L	0.53 g/g	[12]
	OE: Aomae, Aopyc, *cbbM, prk*; Del: *pdc, ldh, pck*	75 g/L Avicel		70.1 g/L	0.93 g/g	
T. reesei	OE: *carB, carRP, hmg1, crtE*	10 g/L of wheat bran and 15 g/L Avicel with MGDS feed	β-Carotene	286.63 mg/L	–	[32]
M. thermophila	OE: *pdc, adh1, nde*; Del: *ldh1, ldh2, mdh, gpdh, mpd, aldh; pfk-mut*	75 g/L cellulose	Ethanol	24.3 g/L	0.32 g/g	[15]
		200 g/L cellulose		52.8 g/L	0.229 g/g	
		100 g/L corncob in 3 L medium fed with 800 g corncob		39.8 g/L	0.12 g/g	

OE: overexpression; Del: deletion; CAD1: cis-aconitic acid decarboxylase from *Aspergillus terreus*; Aomae: malic acid exporter gene from *A. oryzae*; Aopyc: pyruvate carboxylase from *A. oryzae*; glt-1: glucose transporter from *N. crassa*; ppc1: PEP carboxylase from *E. coli*; mdh: native cytoplasmic malate dehydrogenase; bicA: HCO_3^- transporter from *Synechococcus* sp.; ca: carbonic anhydrase from *Synechococcus* sp; pdc: native pyruvate decarboxylase; ldh: lactate dehydrogenase; pck: PEP carboxykinase; Ctcpp: cellobiose phosphorylase from C. thermocellum; cdt-1: cellobiose transporter from *N. crassa*; bgl2/3: native intracellular β-glucosidases; cbbM: ribulose-1,5-bisphosphate carboxylase–oxygenase from *R. rubrum*; prk: phosphoribulokinase from *S. oleracea*; gal2M: a galactose/glucose transporter from *S. cerevisiae* with N376F mutation; carRP: phytoene synthase/lycopene cyclase from *Mucor circinelloides*; carB: phytoene dehydrogenase from *M. circinelloides*; hmg1:native hydroxymethylglutaryl-CoA reductase; crtE: geranylgeranyl diphosphate synthase from *Xanthophyllomyces dendrorhous*; adh1: alcohol dehydrogenases from *S. cerevisiae*; nde: external NADH dehydrogenase; gpdh: glycerol-3-phosphate dehydrogenase; mpd: mannitol-1-phosphate dehydrogenase; aldh: aldehyde dehydrogenase; pfk-mut: 6-phosphofructo-2-kinase with H233G, E306G, H371G mutation.

Sugar uptake is a critical step for efficient biochemicals and bioethanol synthesis. Manipulation of cellobiose utilization and transport through overexpression of a cellobiose phosphorylase *Mtcpp* and Cdt-1 improves malic acid production on cellulose [31]. Ali et al. identified a high-affinity glucose transporter in *Fusarium oxysporum*. Its overexpression increased the ethanol production from glucose, xylose, and alkaline-treated wheat straws, which are probably attributed to enhanced transport of C5/C6 substrate [33]. Overexpression of a glucose transporter Glt-1 or a cellodextrin transport system (Cdt-1/Cdt-2) from *N. crassa* in *M. thermophila* further improves the ethanol yield by 131% from glucose, and 200% from cellobiose, respectively [7]. Besides, a peptide transporter from *F. oxysporum* also suggested to influence ethanol production whose overexpression gave a 17% increase in ethanol yield [34]. Meanwhile, several genes involved in sugar transport were significantly upregulated in a malic acid hyper-producer *M. thermophila* [30], indicating that a superb sugar uptake might accelerate the metabolic pathway toward biochemicals and bioethanol production.

An efficient carbon flux toward biochemicals and bioethanol synthesis is also an indispensable factor for high-level production. Strengthening the rTCA pathway through the expression of a PEP carboxylase resulted in a 1.09-fold improvement in malic acid titer in *M. thermophila* [30]. Modification of the MVA pathway, the upstream pathways for *β*-carotene production, through overexpression of hydroxymethylglutaryl-CoA reductase HMG1 and geranylgeranyl diphosphate synthase GGS1/CrtE, improved the *β*-carotene synthesis in *T. reesei* [32]. Expression of the phosphoglucomutase and transaldolase, which are two key enzymes in glucose metabolism, and pentose phosphate pathway in *F. oxysporum*, improved the bioethanol production up to 20.4 g/L, a 2.06-fold increase compared to the wild-type F3 from glucose [35]. Alleviating the byproduct acetic acid synthesis through deleting aldehyde dehydrogenase is also beneficial for ethanol production in *F. oxysporum* [36]. Turning down the expression of a pyruvate carboxylase gene *pyc* in *M. thermophila* increased ethanol production by 23% using cellobiose as carbon source [7]. Blocking the NADH shuttles from

the cytoplasm to mitochondria significantly increases the ethanol production in *M. thermophila* up to 40.8 times on cellulose [15]. The cellulose degradation and metabolic flux are both important for efficient biochemicals/bioethanol synthesis. How to subtly keep the balance between these factors in fermentation still awaits further development. Furthermore, advanced strategies, for example, the dynamic regulating circuits [37], lifespan and morphology engineering [38], and protein engineering guided strategies [39] which are widely used in bacteria and yeasts, need to be developed and applied in cellulolytic fungi to realize efficient CBP from agricultural byproducts.

Construction of a fungal–bacteria/yeasts consortium for efficient biorefinery from agricultural byproducts

Although using a one-pot fermentation strategy to produce biochemicals from agricultural byproducts by one strain has its advantage of cost-effectiveness and saving the labor, complicated genetic engineering and excess metabolic burden in one microorganism might not lead to promising results owing to unsatisfactory efficiency. Therefore, an alternative strategy of synthetic microbial consortia by using the cellulose-degrading fungi and biochemical-producing strain was also suggested, which was considered to perform more complicated tasks [40]. A cellulolytic fungus–bacteria consortium were first combined to produce isobutanol from lignocellulosic feedstocks by Minty et al. [41]. *T. reesei* was used as a cellulase producer to hydrolyze lignocellulosic substrates, and co-culture of an engineered *E. coli* enables the production of isobutanol with a titer of 1.88 g/L from pretreated corn stover. An oxygen gradient was formed by using a biofilm membrane reactor, 9.8 g/L ethanol production was achieved by combining *T. reesei*, *S. cerevisiae*, and *Scheffersomyces stipitis*, probably owing to the optimal oxygen requirement in one pot [42]. Implementing a calcium alginate-immobilization strategy meets the compartmentalized oxygen requirement of *Trichoderma asperellum* and lactic acid producer *Lactobacillus paracasei*, realizing a 53.5 g/L lactic acid production on Avicel and 14.9 g/L on cornbob [43]. Moreover, co-culture of *T. reesei* with: *L. pentosus*, *Rhizopus delemar*, *R. oryzae*, *Ustilago maydis*, *Talaromyces albobiverticillius*, and *S. cerevisiae*, enables direct production of: lactic acid [44,45], fumaric acid [45], glucaric acid [46], itaconic acid [47], and pigments [48] from lignocellulosic substrates (Table 2), providing promising strategies for CBP from agricultural byproducts. Other co-culture systems via cellulolytic bacteria or recombinant cellulase-producing yeasts have also been reported – the author found related information in a recent review [40].

The consortium-based CBP can combine the individual advantages of cellulose deconstruction and bioproduct synthesis, to avoid complicated genetic engineering and heavy metabolic burden [49]. However, the sugar release rate from the lignocellulosic substrate by cellulolytic fungi encounters the rapid synthesis of bioproducts. Thus, it is of interest to make the compatible ratio of the sugar flux in the consortium to achieve efficient CBP. Moreover, owing to the different preferences of microorganisms for temperature, pH, and oxygen, individual or sequential inoculation is needed to achieve the highest yields [43]. Moreover, current researches using biofilm-based reactor and alginate-immobilization meet the different oxygen requirement in the CBP system and give promising results. Further studies still need to focus on the development of novel reactor which harbor efficient mass transfer, separated oxygen distribution, and individual temperature control to fully meet the different requirement of microorganism in CBP. Besides, other strategies including compartment and immobilization of the cellulose-degrading fungi and biochemical-producing strain by hydrogel or entrapped by other materials might enhance the mass transfer, and would give a clue to satisfy the requirement for efficient CBP by fungal bacteria/yeasts consortia.

Summary

Cellulolytic fungi have attracted attention on the development of an efficient workhorse to transfer agricultural byproducts into valuable-added biochemicals via CBP. Cellulolytic fungi could robustly grow on agricultural byproducts with a low nutritional requirement. Moreover, as eukaryotic organisms, these fungi harbor a strong ability to synthesis and secret proteins with a complex post-translational modification, and have advantages to process intron, making them ideal candidates for genetic engineering. Besides, the concept of CBP, which makes cellulase production, saccharification and biochemical production in one pot, is considered as a labor-saving process with promising perspectives for industrial application. Although several studies have achieved efficient biochemicals synthesis, some disadvantages are still presented. Unlike bacteria and yeast, most cellulolytic fungi lack multiple genetic tools, which make the genetic engineering tedious and difficult to realize. Systematical engineering in cellulolytic fungi might make a heavy metabolic burden, to maintain balance in the fungal growth, cellulase

Table 2. Fungal–bacteria/yeasts consortia for efficient biorefinery from agricultural byproducts.

Fungal consortia	Substrates	Products	Yield	Productivity	Ref.
T. reesei + *engineered E. coli*	20 g/L ammonia fiber expansion pretreated corn stover	Isobutanol	1.88 g/L	62%	[41]
T. reesei + *S. cerevisiae* + *S. stipites*	Undetoxified dilute acid-pretreated wheat straw	Ethanol	9.8 g/L	67%	[42]
T. reesei + *L. pentosus*	50 g/L cellulose	Lactic acid	34.7 g/L	62.40%	[44]
	50 g/L steam-pretreated washed beech wood		15.1 g/L	65.60%	
	50 g/L non-detoxified steam-pretreated beech wood		19.8 g/L	85.20%	
T. reesei + *R. delemar*	40 g/L cellulose	Fumaric acid	6.87 g/L	0.17 w/w	[45]
	20 g/L alkaline pretreated corn stover		0.69 g/L	0.05 w/w	
T. reesei + *R. oryzae*	40 g/L cellulose	Lactic acid	4.4 g/L	0.11 w/w	
T. reesei + *engineered U. maydis*	120 g/L cellulose	Itaconic acid	10.5 g/L	0.134 g/g	[47]
	270 g/L cellulose fed-batch		33.8 g/L	0.156 g/g	
T. reesei + *engineered S. cerevisiae*	15 g/L Avicel	Glucaric acid	0.54 g/L	–	[46]
	15 g/L steam-exploded corn stover		0.45 g/L	–	
T. reesei + *T. albobiverticillius*	Food waste	Pigment	63.8 AU/gds (400 nm)	–	[48]
T. asperellum + *L. paracasei*	60 g/L cellulose	Lactic acid	53.5 g/L	–	[43]
	60 g/L corncob		14.9 g/L	–	

production, and the biochemical synthesis which is the critical steps to achieve efficient CBP. Although fungal bacteria/yeasts consortia provide alternative strategies, the uncoordinated growth and nutrient requirement between different strains still needs to be resolved. Further, continuous studies with new ideas and tools are still required. We hope these will help to improve the performance of cellulolytic fungi in biochemical synthesis from agricultural byproducts.

Biotransformation of phenolic compounds from agricultural byproducts by cellulolytic fungi

Phenolic compounds are organic compounds naturally synthesized by plants, which could be divided into: phenolic acids, flavonoids, stilbenes, coumarins, and lignans according to structural diversities. These natural compounds are widely distributed in agricultural byproducts with abundant bioactive properties for: antioxidant, anti-inflammatory, anticancer, antimicrobial, and antidiabetic activities, etc., indicating their potential use for food additives and pharmaceutical industries [50]. The commonly used strategies for PC extraction from agricultural byproducts mostly recover free or conjugated PC, while a large proportion of unextractable PC is trapped or bounded in the polymer matrix, underestimating their health benefit [51].

A growing number of studies are concerned on effective PC extraction, especially on unextractable or bounded PC (BP) [52]. Among that, fermentation-aided extraction shows great advantages of low cost, high efficiency, and being environmental-friendly [53]. The assimilation and degradation of the polymer matrix in agricultural byproducts by fungal hydrolyzing enzymes break the interaction between PCs and macromolecules. Improved recovery of PC from agricultural byproducts would be achieved after fermentation, with changed compositions and higher biological activities, showing potential interest in agricultural byproducts valorization. Here, we summarized the recent progress of cellulolytic fungi fermentation on PC recovery. The mechanism for BP release and the potential gene networks involved in biotransformation have also been elucidated.

Improving the bio-accessibility of phenolic compounds by cellulolytic fungi

The unextractable or BP are largely presented in fiber-rich agricultural byproducts, either linked to the macromolecule or trapped in the polymer matrix, which is hardly released by traditional solvent extraction [6, 54]. Different microbes, including bacteria, yeasts, and fungi, have been applied to ferment agricultural byproducts and recover PCs. The yield and its biological functions varied depending on the strain and substrate used [4]. Among them, cellulolytic fungi such as *Trichoderma* spp. and *Aspergillus* spp. are good candidates for fiber-hydrolyzing enzyme production, and could robustly grow on lignocellulosic byproducts. The cellulase cocktail produced by these fungi has been widely used for lignocellulose hydrolysis and PC extraction from agricultural byproducts [1]. Besides, cellulolytic fungi are also suitable candidates for solid-state fermentation, which is the commonly used strategy for

enhancing the bio-accessibility of PC in agricultural byproducts [55]. The superb advantages of cellulolytic fungi attracted wide application in agricultural byproducts valorization, suggesting their great potential for value-added biotransformation by these fungi.

Rice bran, which is a by-product of rice refining, natively contains abundant PCs but mostly in its bounded form [56]. The traditional solvent extraction only recovers a small part of PC; however, a fermentation treatment with *Rhizopus oryzae* significantly increased the total phenolic content (TPC) [57]. Fermentation of the insoluble DF from defatted rice bran with *Trichoderma viride* released TPC to 5.55 ± 0.13 mg GAE/g DW, with ferulic acid being most abundant (1.89 mg/g) [13]. It is worth noting that the BP released after fermentation is more abundant than an alkaline-treated group, and exhibits more robust antioxidant activities, indicating the outstanding performances of cellulolytic fungi in BP recovery. Moreover, the application of: *Rhizopus* spp., *Aspergillus* spp., *Trichoderma* spp., *Monascus* spp., and other combined microbial consortia to release BP from agricultural byproducts have also been achieved in recent years (Table 3). The releasing mechanism and synergism work of different hydrolyzing enzymes during the fermentation have also been studied.

Mechanism of phenolic compounds release during fermentation

Cellulolytic enzymes are important enzymes for BP release from agricultural byproducts. In most studies, the total cellulase activities (FPase), endo-glucanase (CMCase), and β-glucosidase significantly show a positive correlation with TPC, which further gives better antioxidant activities after fermentation treatment [61, 66, 73]. Moreover, it is suggested that the combination of *Monascus* fermentation and cellulase hydrolysis further improved the BP release than fermentation-treated only, which might be attributed to the higher decomposition of the cellulosic substrate [68]. *Trichoderma* spp. is an excellent cellulase producer but lacks efficient β-glucosidase activities. Combined fermentation of *T. viride* and *A. niger* gained significantly improved β-glucosidase activities, and promote efficient PC release from navel orange peel and carrot [65,66]. It is noteworthy that β-glucosidase mainly functions on the cleavage of disaccharides, which are released from the cellulosic matrix and lead to an end-product inhibition of exo- and endo-glucanase [74]. Improved β-glucosidase would result in a more efficient hydrolysis of cellulosic substrate, and promote the release of PC. In addition, conjugated PC which is linked to other saccharides is also widely distributed in the extraction [52]. These compounds usually exhibit lower bioactivities than the free form due to less hydroxyl group exposure [75]. The β-glucosidase secreted by cellulolytic fungi was also suggested to cleave the phenolic glycosides between PC and sugars, forming the PC aglycone with higher bioactivities [2]. Fermentation of apple peels with *A. niger*, a well-known β-glucosidase producer, decreased the quercetin glycosides but increased its aglycone form, giving higher antioxidant properties [58]. *E. cristatum* mediated fermentation of soybeans shows higher β-glucosidase activities and transfers glucosides isoflavone to their aglycones [73]. Besides, increased free PC was achieved by *A. niger* fermentation of Mexican mango seed, which releases PC aglycone from its glycoside form [11].

Except for cellulases, cellulolytic fungi could also produce plenty of hemicellulose-degrading enzymes to break the polymer matrix for better PC release. Generally, hemicellulose is the second rich component following cellulose, mainly connecting with different PCs (ferulic acid, coumaric acid) and forming complex sheet structures around the cellulose. Owing to the complicated structures formed by cellulose and hemicellulose, hemicellulase leads to a more complete hydrolysis of lignocellulose substrate by improving the accessibility of cellulase [76]. The combination of hemicellulase with cellulase leads to a more efficient PC extraction [77]. A positive correlation between xylanase activity and TPC was also suggested by a study of oat fermentation by *M. anka* [78]. Besides, an increased amount of xylanase treatment improves the ferulic acid release by ferulic acid esterase from oat hulls [79]. Despite the loss of structures and enhancement in bioaccessibility of PC, some auxiliary enzymes such as ferulic acid esterase are also responsible for the cleavage of ferulic acid and other hydroxycinnamic acids linked to the sugar chains, especially from cereals and straws [2]. The expression of two feruloyl esterases from *Aspergillus* spp. in *T. reesei* leads to the efficient release of ferulic acid from wheat bran [80]. Recovery of 1.89 mg/g DW ferulic acid was achieved by fermentation of insoluble DF from defatted rice bran with *T. viride*, but not in the alkali-treated group [13], indicating the critical functions of microbial ferulic acid esterase for PCs release from agricultural byproducts. Moreover, other hydrolytic enzymes, including pectinase, amylase, and protease, were also critical for efficient PC recovery from agricultural byproducts during microbe fermentation, and a mixed fermentation by different strains with varied enzyme activities also benefits PC release [1, 81].

Table 3. Recent advances of cellulolytic fungi aided extraction of phenolic compounds.

Fungi	Substrate	Condition	Effect	Ref.
A. niger	Apple peel	30 °C; seven days	Increased TPC (fourfold), TFC, and antioxidant activity; quercetin glycosides decreased with increased concentration of quercetin aglycone	[58]
A. niger	Avocado seed	30 °C; 312 h	Increased TPC (14.56 mg GAE/g), antioxidant activity	[59]
A. niger	Mexican rambutan peel	25 °C; 12/24 h	Increased TPC (104.243–185.396 mg/g), EA (3.44–13.901 mg/g), antioxidant activity	[60]
A. niger	Mexican mango seed	30 °C; 20 h	Increased TPC (984–3288 mg GAE/100 g), antioxidant activity. BP decreased with increased free PC. PC aglycone released from glycoside from by fermentation	[11]
A. niger	*Apocynum venetum* L.	28 °C; 12 days	Increased TPC (206.84–314.58 mg GAE/g DM), improved antioxidant activity, inhibition against metabolic syndrome-associated enzymes.	[61]
Aspergillus ibericus	Vine trimming shoots	25 °C; seven days	Increased TPC (2.9-fold), antioxidant activity	[62]
Aspergillus japonicus	Chestnut	30 °C; seven days	Increased ellagic acid (0.48–2.04 mg/g DM)	[63]
Aspergillus oryzae	Barley bran	25 °C; seven days	Increased TPC (1.23–14.32 mg GAE/g) and antioxidant ability.	[64]
T. viride	Insoluble dietary fiber of defatted rice bran	28 °C; four days	Released BP (5.55 ± 0.13 mg GAE/g DW) with ferulic acid most abundant (1.89 mg/g DW), improved antioxidant activity	[13]
T. viride + *A. niger*	Insoluble dietary fiber in carrots	28 °C; three days; inoculation ratio = 1:1	Released BP (80.8759 mg GAE/10 g DW) with abundant p-coumaric acid (167.709 μg/g), which is positively correlated with xylanase activity and beta-glucosidase. Improved antioxidant activity and α-amylase inhibitory activity is observed after fermentation	[65]
T. reesei + *A. niger*	Insoluble dietary fiber of navel orange peel	28 °C; 28 h; inoculation ratio = 3:1	Released BP (6.98 mg GAE/g DW) with abundant p-coumaric acid (1885.16 μg/g), which is positively correlated with cellulase, xylanase, and beta-glucosidase activity. Improved antioxidant activity is observed after fermentation	[66]
R. oryzae	Defatted rice bran	30 °C; five days	Increased TPC (618.7–1061.8 mg GAE/100 g DW), free PC, BP, and antioxidant activity	[57]
R. oryzae + *A. ibericus*	Oilseed cakes	25 °C; seven days	Increased TPC and antioxidant activity	[67]
Monascus anka	Oats	30 °C; 14 days	Increased soluble-free fractions (0.09–3.31 mg GAE/g DW), insoluble-bound fractions (0.18–0.71 mg GAE/g DW)	[68]
M. anka + *Bacillus subtilis*	Oats	30 °C; 12 days; inoculation ratio: 2:1; *B. s* was inoculate four days delay after *M. anka* inoculation.	Increased TPC (1.18–27.94 mg GAE/g DW) with positive correlation with α-amylase, β-glucosidase, and cellulase. Increased free, bound and conjugated phenolic fragments, improved antioxidant activity.	[69]
M. anka + *S. cerevisiae* + *B. subtilis*	Corn kernels	30 °C; 14 days; *S. c* and *B. s* were inoculated after six days fermentation	Increased TPC (1.40–25.31 mg/g), antioxidant activity	[70]
M. anka + *S. cerevisiae* + *B. subtilis*	Corn seeds	30 °C; 14 days; *S. c* and *B. s* were inoculated after 12 days fermentation	Increased TPC (1.39–31.36 mg GAE/g), antioxidant activity	[71]
Monascus purpureus	Coix seed	30 °C; 10 days	The tocols, γ-oryzanol, and coixenolide contents increased approximately 4, 25, and 2 times with improved antioxidant activity and inhibiting lipid oxidation	[72]
Eurotium cristatum	Soybeans	28 °C; 15 days	Increased TPC (2.716–5.205 mg GAE/g) with positive correlation with α-amylase, β-glucosidase, cellulase, and protease. Glucosides isoflavone transfer to aglycones by fermentation; improved antioxidant activity.	[73]

TPC: total phenolic content; TFC: total flavonoid content; GAE: gallic acid equivalents; EA: ellagic acid; BP: bounded phenolic compounds; PC: phenolic compounds.

Despite increased TPC, the composition of PCs after fermentation is also changed, and the abundant formation of high-antioxidant PC such as *p*-coumaric acid, vanillin, and gallic acid, etc., might contribute to improved antioxidant activities of total PC extraction [2, 13], indicating that the metabolism of PC by cellulolytic fungi is also important for higher bioactive PC extraction [82].

Metabolism and biotransformation of phenolic compounds in cellulolytic fungi

Phenolic compounds with free hydroxyl group are toxic to the microorganism in a concentration-dependent manner; however, the microbes have also evolved subtle metabolism flux to assimilate and utilize PCs. A series of catabolism including: hydroxylation, oxidation, methylation, and demethylation, have been conducted by microbial enzymes to generate other compounds with varied properties [83]. These PCs would finally be catalyzed to the central intermediates such as protocatechuic acid and catechol, and then be subjected to ring fission to the TCA cycle [84]. In bacteria, great achievements have been made in the characterization of specific regulatory pathways and the synthesis of high-value aromatic compounds by rational engineering [85]. Increasing studies have also been conducted on the unraveling of key enzymes and pathways of phenolic metabolism in filamentous fungi, which shares both similarities and differences compared to that in bacteria and yeasts [84].

The biotransformation of ferulic acid to vanillin was achieved by a two-step fermentation by the two fungi *A. niger* and *Pycnoporus cinnabarinus* [86]. Although the *de novo* biosynthesis of vanillin in yeasts has been achieved by combining the key enzymes from bacteria in the same period [87], the enzymes involved in vanillin synthesis in fungi have not then been elucidated. The C-3′ dehydroxylation of rutin to form kaempferol-3-rutinoside was conducted by fermentation with *A. awamori*. However, this biotransformation seems to be weak in that the main compound after fermentation is quercetin, which is the deglycosylated form of rutin [88]. Moreover, the metabolism of 3-phenoxybenzoic acid and vanillic acid in different cellulolytic fungi has also been tested, among them: *Aspergillus* spp., *Trichoderma* spp., *Penicillium* spp., *Fusarium* spp., and *Neurospora* spp. exhibited prominent performance in assimilating these compounds and transforming into other PCs [89,90]. Besides, novel PCs could be bio-transformed by fermentation of agricultural byproducts. Biodegradation of naringin and hesperidin to their lower molecular weight compounds has been observed after the fermentation of citrus residues by *Paecilomyces variotii* [91]. However, the monomer gallic acid is completely degraded after fermentation, perhaps by a ring cleavage to the TCA cycle, as suggested, in other fungi [84, 92]. An increased amount of chlorogenic acid was achieved through the fermentation of leaves of *Psidium guajava* L. by *M. anka* and *Bacillus* spp., but how these compounds could be formed during fermentation is hard to elucidate considering that it is not presented in the bound form [93]. Moreover, the fermentation of oats by *M. anka* shows increased amounts of vanillic acid, which is the downstream metabolite of ferulic acid released from its bounded form by fermentation [78, 94]. Fermentation of insoluble DF of navel orange peel by *T. viride* and *A. niger* increased the content of protocatechuic acid, which is the intermediate metabolite of most aromatic compounds, indicating that these PCs were actively metabolized during fungi fermentation [66]. Although the hydroxylation and decarboxylation of some PCs have been observed in a few species [95], their accurate assigned genes in catabolism have been hardly confirmed.

In recent years, the uncovering of genomic and transcriptomic data in industrial-relevant fungi and the application of genetic tools enable further exploration and clarification of specific genes and enzymes in filamentous fungi, mainly in *Aspergillus* spp. The protocatechuate and the catechol branches from benzoate and salicylate to the TCA cycle have been re-assayed in the model fungus *Aspergillus nidulans* using comparative proteomics, transcriptomics, and gene-replacement assays, which assigned most of the steps of two pathways in this fungus [96]. The functional genes in benzoate catabolism have also been identified in *A. niger* recently, which shares similarities with that in *A. nidulans*. The two-step hydroxylation of benzoic acid to protocatechuic acid is conducted by benzoate-4-monooxygenase (BphA) and *p*-hydroxybenzoate-*m*-hydroxylase (PhhA), respectively. Further metabolism of protocatechuic acid to 3-oxoadipate pathway is also conducted directly by a protocatechuate 3,4 ring-cleavage dioxygenase (PrcA), or a two-step catalysis with protocatechuate hydroxylase (PhyA) and hydroxyquinol 1,2 ring-cleavage dioxygenase (HqdA) [97,98]. A double deletion mutant (Δ*prcA*Δ*phyA*) could efficiently accumulate protocatechuic acid from diverse aromatic compounds, suggesting its potential for industrial-scale protocatechuic acid production as a precursor for other chemicals synthesis [98]. Moreover, the catabolism of salicylic acid to another intermediated aromatic compound, catechol in *A. niger* has also been characterized. Salicylic acid is first hydroxylated by a salicylate

hydroxylase (ShyA) and further cleaved by a catechol 1,2-dioxygenase (CrcA) to produce *cis*, *cis*-muconic acid, which is an important intermediate for: nylon polyethylene terephthalate (PET), polyurethane, resins, and lubricants synthesis [99].

The degradation of hydroxycinnamic acids caffeic acid, ferulic acid, and *p*-coumaric acid to their benzoate forms (e.g., protocatechuic acid, vanillic acid, and *p*-hydroxybenzoic acid) in *A. niger* has been suggested by a series of enzymes involved in CoA-dependent β-oxidative pathway through a transcriptome data analysis [100]. However, the function of assigned genes was only tested by a plate growth assay, which still awaits further experimental verification. Moreover, the metabolism of vanillin in *A. niger* has been characterized through oxidizing to vanillic acid by a vanillin dehydrogenase (vdhA) and then hydroxylating to methoxyhydroquinone by vanillate hydroxylase (vhyA) [101]. However, the ability of different species to metabolize PCs is different; although some pathways are highly conserved, others have changed. The demethylation of vanillic acid to protocatechuic acid has been observed in *A. oryzae*, *Aspergillus ustus*, and *Aspergillus fumigatus*, but not in *A. niger*, even in a *vhyA* deleted mutant [89, 101]. *Trichoderma* spp. prefers to convert vanillic acid to vanillin and vanillyl alcohol [89], and the homologs of genes in the methoxyhydroquinone pathway did not exist in this species. Although the clarification of functional genes in PCs mainly focused on *A. niger* and bacteria, it also provides novel clues for the characterization of PCs metabolism in other fungi [84].

Summary

In recent years, cellulolytic fungi have been widely used as a tool for PCs recovery from agricultural byproducts. After fermentation treatment, the entrapped BP was released by fungal hydrolyzing enzymes, and the composition of phenolic component was also changed due to the rapid metabolism by fungi. This strategy shows a prominent advantage in the recovery efficiency, as well as its higher biological properties than the traditional chemical method. Besides, the fermentation aided strategy is also acceptable as a green process which shows further perspectives in food and pharmaceutical industry. Current studies point out the indispensable role of cellulase, xylanase, and glucosidase on BP release, and characterize the potential biotransformation of PCs and related gene networks during the fermentation. However, owing to the diversified distribution of PCs and poorly characterized genetic pathways in fungi, it is still hard to fully elucidate the mechanism of cellulolytic fungi on PCs biotransformation. The deepen exploration of fungal PCs metabolism further leads to a comprehensive understanding of the function of cellulolytic fungi in agricultural byproducts valorization, and it also provides promising strategies to engineer cellulolytic fungi for valuable PCs bio-transformation from agricultural byproducts.

Modification of dietary fiber from agricultural byproducts by cellulolytic fungi

Dietary fibers are the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption, including: polysaccharides, oligosaccharides, lignin, and associated plant substances [102]. DFs are generally considered functional nutrients with important healthy benefits by reducing the risk of: cardiovascular disease, coronary heart disease, obesity, prediabetes, type-2 diabetes (T2DM), and some types of cancer [4, 103]. The high-DF diet is increasingly accepted by customers recently, with a daily intake of 25–30 g DF as suggested [104]. DF could be categorized as soluble dietary fiber (SDF) and insoluble dietary fiber (IDF) according to its structure and water solubility [105]. IDF mainly consists of cellulose and hemicellulose, which is mainly linked by β-(1→3), β-(1→4), and β-(1→6) bonds in the main sugar chain [106,107]. The sugar chain in IDF is mostly linear type with a few side chains, the association between different sugar chains is mainly formed by dense hydrogen bonds, forming a hydrophobic and crystalline structure [107]. While for SDF, pectin, β-glucan, and other oligosaccharides with diverse β-(1→3), α-(1→4), α-(1→6), and α-(1→2) bonds are representatives. The solubility of SDF is mainly structure-dependent, low-molecular weight, and highly branched structures endow a higher solubility [107]. Owing to its higher water-solubility and structural characteristics, SDF prefers to absorb heavy metals and exerts biological functions in its soluble form by regulating blood cholesterol levels, protecting against different cancers, and anti-inflammatory activities, suggesting the importance of SDF than IDF for health benefit. These reports strongly indicate the broader application of SDF as functional food additives [108]. However, in most agricultural byproducts sourced DFs such as cereal by-products and fruit peels, IDFs are abundantly presented but the content of SDF is relatively low, underestimating their health benefits [109]. Numerous studies were conducted to convert IDF to SDF and improve their health benefits. Recently, biological strategies especially fermentation-aided conversion of DF have become increasingly attractive due to

their high efficiency and mild process, which is acceptable for food industries [110]. Among that, cellulolytic fungi could secret plenty of hydrolyzing enzymes to break the polymeric structure in agricultural byproducts and exhibit excellent ability in IDF modification, suggesting their important roles in the efficient reutilization of functional DFs from agricultural byproducts. In this section, we focused on the cellulolytic fungi fermentation-mediated DF modification. The individual and synergistic mechanism of fungal hydrolyzing enzymes in the fermentation on DF conversion is illustrated according to recent literature. Besides, the commonality and discrepancy of cellulolytic fungi on DF modification from agricultural byproducts are also summarized and discussed, unraveling the presented bottlenecks and further perspectives in DF modification by cellulolytic fungi for efficient agricultural byproducts utilization.

Hydrolyzing enzymes produced by cellulolytic fungi and their mechanism on functional SDF preparation

Large amounts of hydrolyzing enzymes are produced by cellulolytic fungi in agricultural byproducts fermentation. Cellulase and xylanase are two important kinds of enzymes that function in the solubilization of IDF. Cellulase is a mixture of different types of cellulose-hydrolyzing enzymes, mainly including exo-glucanase, endo-glucanase, and β-glucosidase. These enzymes act synergistically on the β-1-4 glycosidic bond to efficiently degrade cellulose polymers [111]. Xylanase represents a group of xylanolytic enzymes containing endo-xylanase, β-xylosidase, and other accessory enzymes functioning in the cleavage of the sub-chain group in xylan chain [112]. Under the treatment of xylanase, the amount of IDF is decreased due to the solubilization of water-unextractable arabinoxylan [113]. Of note, the hydrolyzing enzymes produced by cellulolytic fungi in fermentation contain a subset of cellulase and xylanase, thus the modification of DF in fermentation is a co-work of different cellulase and xylanase. With the assistance of cellulase and xylanase, the highly crystallized cellulose in agricultural byproducts could be converted to low molecular and amorphous form, which improves its water solubility [114]. Moreover, the hydrolysis of the crystalline structure by these fungal hydrolyzing enzymes would loosen the connection between different compositions, making the DF more porous to hold sugar, water, oil, or heavy metals [16]. Different combinations of cellulase and xylanase with varied enzyme load leads to the improved yield of SDF with: higher bioactive performance, lower molecular weight, loosened structures, and enhanced biological properties [115,116], indicating a proper enzymes ratio of fungal produced cellulase/xylanase would lead to a better performance in SDF preparation.

Moreover, β-glucanase is also an important enzyme for DF modification. Generally, DFs contain a large proportion of β-glucan, which consists of glucose by β-1,3 and β-1,4 glycosidic bonds. This type of DF exhibits excellent biological activities, but its functions varied depend on its structures [117]. The natural β-glucan in agricultural byproducts usually harbors a high molecular weight, it is extensively composed of cellulose-like stretches with interspaced β-1,3 linkages, finally resulting in partial water solubility [106]. The cleavage of β-glucan by specific β-glucanases reduces the molecular weight and increases its water solubility, the exposed active sites by forming highly branched structures permit strong bioactive properties toward tumors [117]. It is also suggested that an optimal molecular weight ranging from 20 to 500 kDa shows a significant bioactive activity [118]. Thus, the degradation of high-molecular DF by β-glucanases also benefits the extraction of bioactive SDF. During the agricultural byproducts fermentation, fungal β-glucanases were usually produced together with other cellulase and xylanase, the cellulase produced by *Trichoderma* spp. also exhibits activities toward β-1,3-glucan [119,120]. Zadeike et al. [121] used a cellulase mixture containing β-glucanase activities to decompose rice bran, achieving higher SDF content and enhancing the degradation of β-glucan. Besides, the improved bread quality and reduced crumb firmness were also observed from β-1,3-glucanase treated wheat, which might be attributed to the partial degradation of β-glucans [122]. These studies all indicate a critical role of β-glucanase in efficient and highly active SDF extraction from agricultural byproducts in cellulolytic fungal fermentation.

Effect of cellulolytic fungi fermentation on dietary fiber modification

The complicated and coordinated hydrolyzing enzymes produced by cellulolytic fungi endow their robust growth and degradation of agricultural byproducts, making cellulolytic fungi ideal candidates for DF modification. The fermentation of defatted rice bran by *T. viride* increased the SDF content from 10.5 g/100 g to 33.4 g/100 g [123]. Although the Fourier transform infrared spectroscopy (FTIR) and X-ray indicate similar structures of amorphous polysaccharides in SDF before and after fermentation treatment, scanning electron microscopy (SEM) shows a loose spatial structure,

which might facilitate higher hydration and adsorption properties [123]. Fermentation with a *Penicillium* sp. resulted in reduced high-molecular weight SDF and increased proportion ranging from 5 kDa to 130 kDa [108], which is a promising molecular weight with higher bioactive properties as suggested by Dai et al. [118]. Besides, the modified SDF after fermentation shows higher TPC, probably attributed to the release of PC from the fibrous matrix of IDF [124]. Other cellulolytic fungi including *Monascus* spp., *Penicillium* spp., and *Aspergillus* spp. have been applied to ferment: okara DF [125], potato pomace [126], seed residue [108], orange peel [127], and grapefruit peel [16] to achieve higher SDF yield and better properties. The detailed information has been listed in Table 4.

It is clearly indicated that different species would give diversified results in DF modification, and the results achieved by different studies are difficult to compare due to differences in substrates and strains used. However, using cellulolytic fungus with a higher cellulase-producing capacity might endow a better performance in DF modification. Co-culture of two cellulolytic fungi *A. puulaauensis* and *Cochliobolus kusanoi* resulted in improved cellulase activities and achieved higher SDF yield compared to the single strain fermentation [130]. Besides, co-culture of a cellulase producer *T. reesei* and a β-glucosidase producer *A. niger*, which has been reported for higher cellulase activities, has also been applied for the DF extraction from navel orange peel [127]. Modified SDF with higher bioactive properties was achieved after fermentation, suggesting its promising characteristic as an additive for jelly production. Moreover, the supplement of cellulase dramatically improved the functional properties of fermented SDF from rice bran by lactic acid bacteria and yeast [116], indicating that efficient hydrolysis of agricultural byproducts by cellulase is important for high-bioactive SDF preparation.

Despite the importance of cellulase in cellulolytic fungi for DF modification, it is worth noting that an optimal fermentation time is also required for the highest SDF preparation [123]. Long-period fermentation would result in excessive degradation and assimilation of SDF by fungi. Moreover, in fermentation, the moment for the highest cellulase activities cannot guarantee the highest SDF yield. In the cases of fermentation by *T. viride* and *N. crassa*, the highest SDF yield was achieved before 48 h [128,129]. But the cellulase production by these two fungi in the early 48 h is relatively low. Although numerous studies concern the isolation of an efficient cellulose-degrading strain [16, 130], the correlation of cellulase activities and SDF yield during the agricultural byproducts fermentation had not been studied.

Summary

The DF in several agricultural byproducts such as rice bran, fruit peels mostly presented as insoluble form. Cellulolytic fungi could secret hydrolyzing enzymes to break down the polymer matrix and converse rigid IDF to functional porous SDF, achieving valuable-added reutilization of agricultural byproducts. Current studies indicate that the co-work of cellulase and xylanase is important for DF modification. The synergism of different enzymes in fermentation resulted in decreased molecular weight and improved biological activities. Meanwhile, cellulolytic fungi-aided DF modification is considered as a green process, which is more acceptable for food industries than the chemical method. However, the application of fermentation on DF modification also has drawbacks such as the long period for fermentation, and the effect of fungi on different substrates might change. Besides, current studies mainly focused on the biological characteristic of modified SDF, while the mechanism of enzymes and fungi on the structure and function changes has only been superficially studied. Further experiment is required to give a deeper understanding of the role of cellulolytic fungi in efficient SDF preparation, which further helps to realize high-level recovery of functional SDF from agricultural byproducts.

Conclusions and perspectives

Agricultural byproducts generally contain large amounts of valuable components but are mostly under poor exploration. Their complicated and intertwined structures formed by polysaccharides, proteins, and other macromolecules make these components difficult to extract and utilize. Cellulolytic fungi are native producers of fiber hydrolyzing enzymes, enabling their robust growth and breakdown of fiber-rich agricultural byproducts to release functional components. Meanwhile, their ability to assimilate lignocellulosic substrates makes them promising candidates to bio-transform agricultural byproducts to other high-value compounds. This study systematically reviewed the value-added biotransformation of these agricultural byproducts by cellulolytic fungi. Current achievements using cellulolytic fungi to utilize agricultural byproducts for: biochemicals/biofuels production, PCs biotransformation, and DF modification are comprehensively discussed here (Figure 3), providing novel insights into the importance of cellulolytic fungi in value-added biotransformation from agricultural byproducts.

It is noteworthy that fiber-hydrolyzing enzymes secreted by cellulolytic fungi are important factors for efficient biotransformation of agricultural byproducts.

Table 4. Effect of cellulolytic fungi fermentation on dietary fiber modification.

Fungi	Substrate	Condition	Effect	Ref.
T. viride	Defatted rice bran	Inoculum: 10% (v/v); pH = 5.8; time: 41 h	SDF increased from 10.5 g/100 g to 33.4 g/100 g with improved WHC, OHC, WS, CAC, loosen structure, complex monosaccharides composition.	[123]
T. viride	Tea residues	Inoculum: 10.34% (v/v); pH = 5.46, time: 43.59 h	SDF increased from 4.3 g/100 g to 31.56 g/100 g with higher uronic acid content, crystallinity (23.11% vs. 17.36%), thermal stability, heavy metal binding capacity, and complex monosaccharides composition	[128]
N. crassa	Okara dietary fiber	Inoculum: 5.5% (v/v); time: 2 d; temperature: 28 °C	SDF increased from 2.24 g/100 g to 6.88 g/100 g, IDF decreased from 63.72 g/100 g to 29.68 g/100 g	[129]
N. crassa + *Lactobacillus bulgaricus*		Inoculum: equal mixed 5.5% (v/v); time: 2 d; temperature: 30 °C	SDF increased from 2.24 g/100 g to 7.69 g/100 g, IDF decreased from 63.72 g/100 g to 23.55 g/100 g, modified DF shows damaged structure, improved α-AAIR and GDRI	
M. anka	Okara	Inoculum: 10% (v/v); time: 7 d	SDF increased from 4.3 g/100 g to 7.7 g/100 g, IDF decreased from 73.5 g/100 g to 66.5 g/100 g, modified DF shows improved WHC, OHC, SC	[125]
M. purpureus	Potato pomace	Inoculum: 10% (v/v); time: 7 d	SDF increased to 114.8 mg/g with loosen structure	[126]
Aspergillus puulaauensis + *Cochliobolus kusanoi*	Tea residues	Inoculum: 5% (v/v); time 112.07 h; pH = 4.58; ratio = 2.46:1	SDF increased from 11.66 g/100 g to 26.47 g/100 g, with decreased Mw and better OHC, WHC and nitrite ion adsorption capacity	[130]
A. puulaauensis		Inoculum: 5% (v/v); time 112.07 h; pH = 4.58	SDF increased from 11.66 g/100 g to 18.82 g/100 g g/100 g, with decreased Mw and better OHC, WHC and nitrite ion adsorption capacity	
Cochliobolus kusanoi		Inoculum: 5% (v/v); time 112.07 h; pH = 4.58	SDF increased from 11.66 g/100 g to 17.55 g/100 g, with decreased Mw and better OHC, WHC and nitrite ion adsorption capacity	
Penicillium sp. YC49	Camellia seed residue	Time: 4 d; pH = 7.1; ratio of CSR to culture medium = 1:25	SDF increased from 10.67 g/100 g to 16.22 g/100 g, IDF decreased from 64.60 to 53.21, modified SDF shows improved WHC, OHC, CAC, pancreatic lipase inhibition capacity, and bile acid binding capacity.	[108]
T. reesei + *A. niger*	Navel orange peel	Inoculation ratio: 3:1; pH = 6.5	Modified SDF shows loose structure, increased WHC, OHC, CAC, and GAC. Jelly containing modified SDF shows higher hardness, better gumminess and chewiness.	[127]
Penicillium sp. YZ-1	Grapefruit peel	Inoculum: 12% (v/v); feed liquid ratio = 1:30; time: 40 h	SDF increased from 6.71 g/100 g to 16.04 g/100 g, IDF decreased from 56.51 g/100 g to 42.83 g/100 g g/100 g. Modified SDF has increased WHC, WS, SC, OHC, CAC, BSAC, and LI.	[16]

WHC: water-holding capacity; OHC: oil-holding capacity; WS: water solubility; CAC: cholesterol absorption capacity; α-AAIR: α-amylase activity inhibition ration; GDRI: glucose dialysis retardation index; SC: swelling capacity; GAC: glucose adsorption capacity; BSAC: bile salt adsorption capacity; LI: lipase inhibition.

Application of high-level cellulase-producing strains resulted in better performance in BP release and SDF preparation [61, 130]. Engineered *M. thermophila* with higher bioethanol production from lignocellulosic substrates permits their higher cellulase output [15]. But the exact mechanism and coordinated networks between cellulase production and value-added biotransformation are difficult to elucidate. Despite that, current researches have also focused on the isolation of novel cellulolytic fungi with higher cellulase production, or the combination of different microorganisms for better performance in functional compound extraction [16]. However, this strategy is sometimes inefficient, the genetic background and safety of isolated strains still need to be further evaluated. In addition, different hydrolyzing enzymes and auxiliary enzymes work synergistically to degrade polymer matrix, but the enzymes produced by one fungus are sometimes imbalanced for efficient byproducts degradation. Using a fungal consortia or engineering fungi to produce other key enzymes benefit for higher degradation efficiency.

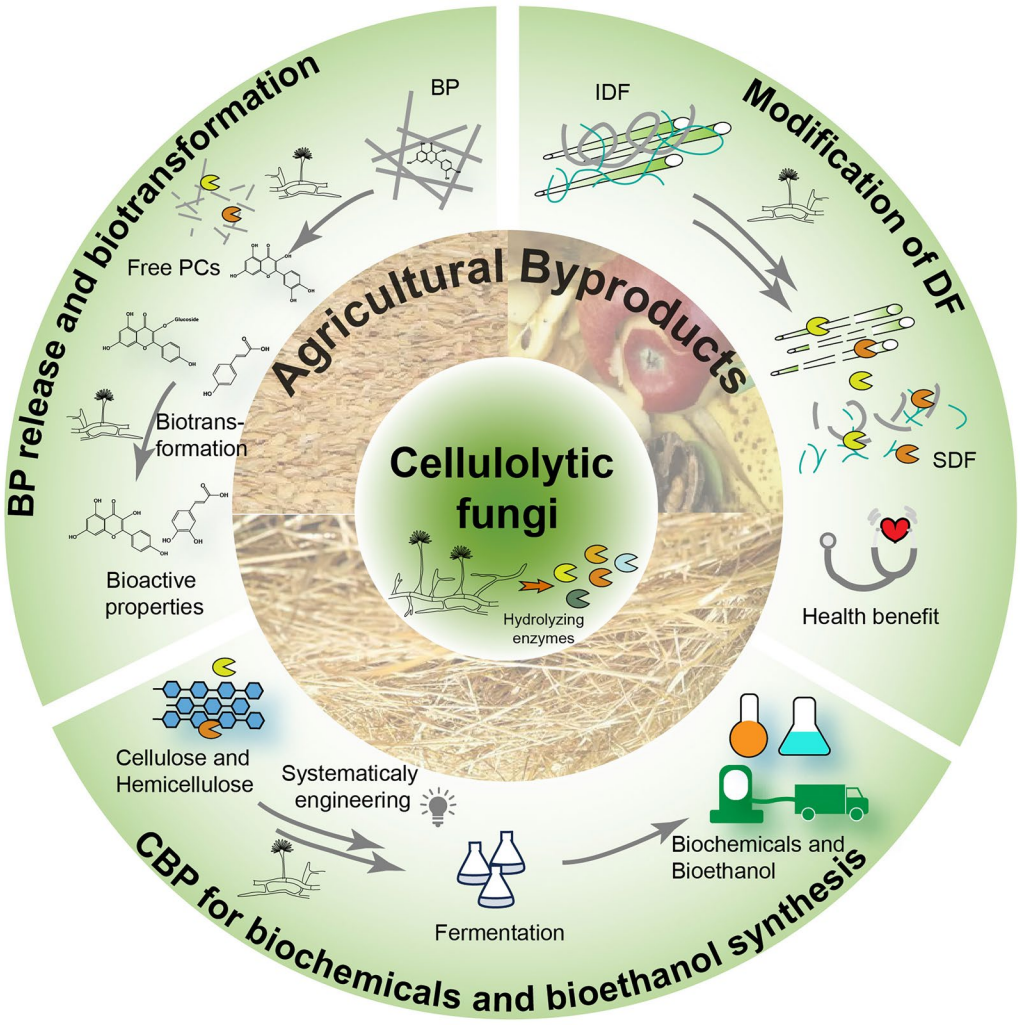

Figure 3. Effect of cellulolytic fungi in agricultural byproducts biotransformation. Agricultural byproducts mainly contain valuable components such as cellulose/hemicellulose, dietary fiber (DF), and phenolic compounds (PCs). Cellulolytic fungi could robustly grow and break the polymer matrix of agricultural byproducts, and could directly produce biochemicals and bioethanol from lignocellulosic agricultural byproducts after systematical engineering. Bounded PC (BP) are extensively presented in agricultural byproducts but are poorly explored. With the assistance of cellulolytic fungi, BP could be released from the agricultural matrix. Meanwhile, successive biotransformation of PC is also conducted to form novel PC with strong bioactive properties. Moreover, functional DF is also present in agricultural byproducts, but most of them are insoluble DF (IDF), underestimating their health benefits. Cellulolytic fungi could break the rigid structure of IDF and convert it to soluble DF (SDF), which is a promising strategy for functional SDF preparation from agricultural byproducts.

Nowadays, genetic manipulating tools have been widely applied in some GRAS cellulolytic fungi. Transcription regulation and expression of hydrolyzing genes in these fungi were stepwise characterized, enabling further rational engineering for efficient cellulase production and lignocellulose degradation [131,132]. Overexpression of functional hydrolyzing enzymes in *A. niger* helps to extract the β-glucan from oat bran [133]. Metabolic engineering of another GRAS cellulolytic fungi *M. thermophila* resulted in efficient CBP from agricultural byproducts to biochemicals [12, 15]. Besides, other GRAS cellulolytic fungus, such as *T. reesei*, has also been engineered for food industries with promising economic effects [9]. These results suggested the importance and prospectives of genetically engineering these GRAS cellulolytic fungi for efficient reutilization of agricultural byproducts.

The development of fungi for natural bioactive compounds production has been highly recommending due to their economic growth conditions, and robust productivity [20]. Although a few achievements have been made to realize value-added biotransformation from agricultural byproducts recently, it is still challenging to the systematical engineering of cellulolytic fungi for efficient agricultural byproducts valorization. Owing to the tedious genetic manipulation procedures and lack of efficient

regulating strategies in cellulolytic fungi, developing novel tools for rate-limited steps and dynamic regulation modules would benefit for the construction of an efficient platform for agricultural byproducts reutilization. The advanced manipulating strategies in bacteria and yeasts, such as: dynamic gene circuits, protein-guided metabolic engineering, or compartmentalized catalytic modules, might still function in cellulolytic fungi, providing guiding perspectives for applying these strategies in cellulolytic fungi. Moreover, a further exploration and understanding of the genetic background and gene functions in cellulolytic fungi would help to establish a well-developed platform for efficient bio-transformation of agricultural byproducts.

Disclosure statement

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