

***Schizophyllum commune*: A Fungal Cell-factory for Production of Valuable Metabolites and Enzymes**

Amit Kumar,^{a,*} Amit Kumar Bharti,^b and Yilkal Bezie^c

Schizophyllum commune is a basidiomycete that is capable of producing different valuable metabolites such as schizophyllan-a polysaccharide, ethanol, and lignocellulolytic enzymes. Schizophyllan finds application in the food industry, pharmacy, and oil recovery. It acts as a non-specific stimulator of immune system. It shows bioactivities such as antineoplastic, antibacterial, anti-cancer, anti-inflammatory, and antiparasitic properties. *S. commune* is capable of producing bioethanol directly in a single step using lignocellulosic biomass. Lignocellulolytic enzymes including cellulase, xylanase, pectinase, laccase, lignin peroxidase, and manganese peroxidase, are also synthesized efficiently by different strains of *S. commune*. Being a good producer of ligninolytic enzymes, *S. commune* has been shown to be effective for the degradation of various synthetic dyes. This article reviews the production of schizophyllan, ethanol, and enzymes and the utilization of *S. commune* for lignocellulose degradation and decolorization of synthetic dyes.

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Contact information: a: Department of Biotechnology, School of Engineering and Technology, Sharda University, Greater Noida, India; b: Department of Natural Resource Management, Pragya, Gurgaon, India; c: Department of Biology, College of Sciences, Bahir Dar University, Bahir Dar, Ethiopia;

* Corresponding author: amit.kumar23@sharda.ac.in

INTRODUCTION

Filamentous fungi are very important for biotechnological processes due to their potential to produce metabolites including enzymes, polysaccharides, organic acids, and antibiotics. *Schizophyllum commune* is a white-rot fungus that synthesizes several metabolites such as lignocellulolytic enzymes, schizophyllan, and ethanol (Alizadeh *et al.* 2021). *S. commune* is an edible mushroom that produces a leathery fruiting body and grows well during the rainy season. It grows on dead and decaying wood (Arun *et al.* 2015). *S. commune* is a basidiomycete fungus that completes its life cycle in 10 days. The fruiting body of *S. commune* shows color variation from gray to whitish, and it is also called a split-gill mushroom (Yelithao *et al.* 2019). It is a most commonly found white-rot fungus that is distributed on all continents with the exception of Antarctica. It is a versatile fungal cell factory that has the capability to produce several valuable metabolites including hydrolytic enzymes, bioethanol, and biosurfactants. *S. commune* is capable of hydrolyzing cellulose, hemicelluloses, and lignin due to its ability to produce lignocellulolytic enzymes such as cellulase, xylanase, pectinase, and lignin-degrading enzymes (Tovar-Herrera *et al.* 2018).

S. commune has also been reported to produce lipase, phytase, and several non-hydrolytic proteins such as lytic polysaccharide monooxygenases and expansin proteins that improve polysaccharides accessibility (Zhu *et al.* 2016; Basso *et al.* 2020). Recently, several functional ingredients including schizophyllan, phenolics, terpenoid compounds and ergosterol have also been found in *S. commune*. The polysaccharide produced by *S. commune* is known as schizophyllan, and this has shown several bioactivities such as immunomodulator, anticancer, antitumor, anti-inflammatory, and antioxidant activities (Wasser and Weis 1999a; Zhong *et al.* 2015; Yelithao *et al.* 2019; Chen *et al.* 2020). Several compounds such as hydroxybenzoic acid, protocatechuic acid, and tocopherol having antioxidant properties are also found in *S. commune*. It also produces iminolactones that are able to suppress the growth of cancer cell lines (Mayakrishnan *et al.* 2013; Basso *et al.* 2020).

The genome of *S. commune* has been sequenced and reported earlier. The database analysis of carbohydrate acting enzymes showed 366 carbohydrates active enzymes in *S. commune*. Of these, 106 were predicted to degrade polysaccharides in lignocellulosic biomass. The lignocellulolytic enzyme pool of *S. commune* is expected to degrade lignocellulosic biomass effectively (Ohm *et al.* 2010; Zhu *et al.* 2016). The efficient utilization of lignocellulosic biomass by *S. commune* may assist the cost-effective production of several valuable products. This review is focused on production of schizophyllan using different substrates under SmF and its medical applications. The present study also reviews the production of industrial enzymes under SSF and SmF, direct ethanol production using lignocellulosic biomass as raw material, lignocellulose hydrolysis to obtain the reducing sugars, and wastewater treatment. Figure 1 shows fruiting body formation in *S. commune* and its growth of on malt extract agar (MEA) and Czapek's yeast autolysate agar (CYA).

SCHIZOPHYLLAN

Production of Schizophyllan

A diversity of microorganisms can produce different exopolysaccharides; this topic has received much attention from researchers (Jayakumar *et al.* 2010). Schizophyllan is a polysaccharide that consists of anhydroglucose monomers, with a β -1,3-linked backbone and single β -1,6-linked glucose side chains at every third residue. It is a non-ionic, water soluble and extracellular polysaccharide that is synthesized by *S. commune*. Currently, the production of schizophyllan is carried out using glucose; the preparation of some purified pharmaceutical and cosmetic products requires a small amount of schizophyllan (Leathers *et al.* 2016). The fermentative production of schizophyllan by *S. commune* can employ several sugars and soluble starch (Kumari *et al.* 2008). The low-cost lignocellulosic residues can be utilized by *S. commune* for the production of schizophyllan (Kumar *et al.* 2015; Sornlake *et al.* 2017; Gautam *et al.* 2018). The production of schizophyllan by different strains of *S. commune* using different substrates including rice hull hydrolysate, corn fiber, date syrup, carboxymethyl-cellulose, glucose, and sucrose, *etc.*, has been reviewed in Table 1.

Leathers *et al.* (2016) studied the production of schizophyllan using corn fiber as substrate. Corn fiber is generated during the wet milling of corn and it is available in large quantity. It is resistant to hydrolysis by enzymes, while it can be utilized easily by *S. commune* for the synthesis of schizophyllan. The yield of schizophyllan was enhanced by

the alkaline pretreatment of substrate and nitrogen source, where malt extract was replaced with low-cost corn steep liquor as a nitrogen source. Untreated and alkaline pretreated corn fiber resulted in 5.4 ± 1.6 g/dm³ and 6.0 ± 0.5 g/dm³ of schizophyllan, respectively, by *S. commune* ATCC38548. Kumari *et al.* (2008) optimized the fermentation medium for maximization of schizophyllan yield. Different carbohydrates such as glucose, sucrose, maltose, lactose, fructose, dextrin, and soluble starch were tested as sources of carbon for *S. commune* NRCM. Among carbon sources tested, sucrose resulted in maximum yield of schizophyllan *i.e.* 3.20 g/L. Similarly, various organic and inorganic nitrogen sources were evaluated for the production of schizophyllan. Among nitrogen sources tested, beef extract (2.62 g/L) showed maximum schizophyllan production. RSM was used to evaluate the effect of variable percentage beef extract and sucrose biosynthesis of schizophyllan. During optimization, schizophyllan yield reached 8.03 g/L compared to initial production of 3.25 ± 0.72 g/L (Kumari *et al.* 2008). The effect of inhibitors, salt concentrations, and detoxification process on schizophyllan production by *S. commune* ATCC38548 was studied. The results showed that the growth of *S. commune* ATCC38548 was inhibited by furfural and sodium ions. The tolerance of *S. commune* ATCC38548 for sodium ions was enhanced by the addition of 0.5 g/L of acetic acid in fermentation media. The activated charcoal was employed for the detoxification of hydrolysate of rice hull. The detoxified hydrolysate resulted in a 2.8-fold increase in the production of schizophyllan (1.30 g/L) compared to rice hull hydrolysate neutralized by NaOH (Shu and Hsu 2011).

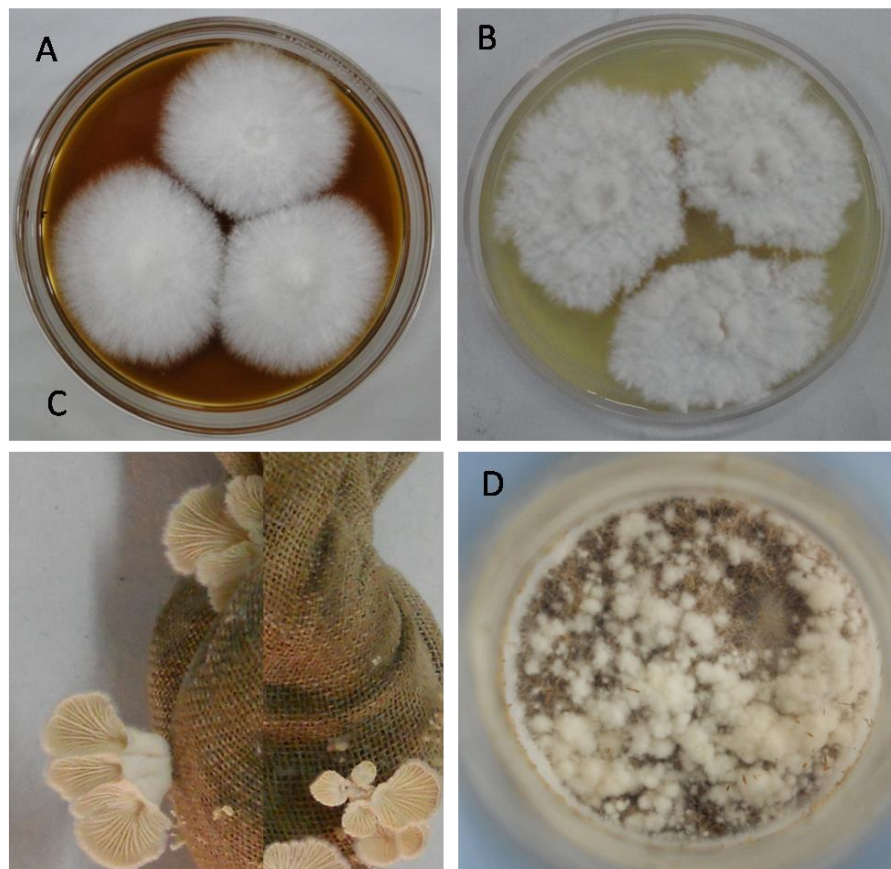


Fig. 1. *S. commune* (A) Growth on MEA at 25 °C; (B) Growth on CYA at 25 °C; (C) Fruiting body formation; (D) Growth on rice straw under SSF

Table 1. Schizophyllan Production from *S. commune* under SmF using Different Substrates

<i>S. commune</i> strain	Carbon source (substrate)	Fermentation Conditions				Schizophyllan (yield)	Ref.
		pH	T (°C)	IP (days)	Agitation (rpm)		
<i>S. commune</i> ATCC38548	Date syrup & corn steep liquor	-	28	8	181	8.5 g/L or 0.12 g/g of date syrup	(Jamshidi <i>et al.</i> 2016)
<i>S. commune</i> ATCC38548	H ₂ O ₂ pretreated corn fiber	-	30	7	240	50 mg/g of corn fiber	(Leathers <i>et al.</i> 2006)
<i>S. commune</i> (CGMCC 5.113)	Carboxymethyl-cellulose	6.5	26	5	150	13.95 g/L	(Li <i>et al.</i> 2011)
<i>S. commune</i> ATCC 20165, <i>S. commune</i> CBS 266.60	Distiller's dried grains with solubles	-	30	8	240	ATCC 20165 strain: 10.1±0.7 g/L CBS 266.60 strain: 12.7±0.1 g/L	(Sutivised sak <i>et al.</i> 2013)
<i>S. commune</i> ATCC 38548	Rice hull hydrolysate	4.5	28	16	-	1.30 g/L	(Shu and Hsu 2011)
<i>S. commune</i> NRCM	Glucose or sucrose	5.5	28	7	180	8.03±1.12 g/L	(Kumari <i>et al.</i> 2008)
<i>S. commune</i> IBRC-M30213	Carboxymethyl-cellulose	5.3	28	7	150	9.97 g/L	(Mohammadi <i>et al.</i> 2018)
<i>S. commune</i> CCMF-795	Sucrose	-	29	5	250	7.2 g/L	(Smirnou <i>et al.</i> 2017)
<i>S. commune</i> ISTL04	<i>Leucaena leucocephala</i> wood	4.5	30	18	150	4.2±0.1 g/L or 0.21 g/g of substrate	(Singh <i>et al.</i> 2017)

T: Temperature, IP: Incubation period, gds: gram dry substrate

Applications of Schizophyllan

Mushrooms are a very important part of nutritional and medicinal foods. They have properties that minimize problems such as hypertension, hypercholesterolemia, and cancer. They also exhibit anti-oxidant and immune-enhancing properties (Saetang *et al.* 2022). Schizophyllan is a polysaccharide that finds applications in various fields such as food processing, pharmacy, and oil recovery. It acts as a stimulator of the immune system. It is also applicable commercially in vaccines preparation and has anti-cancer properties. It can also be used as a bioactive ingredient of cosmetics. Due to its physical properties such as film formation, thermal stability, and high viscosity, schizophyllan can be employed as a biomaterial for various applications (Rau *et al.* 1992; Schulz *et al.* 1992; Zhang *et al.* 2013; Leathers *et al.* 2016). Schizophyllan also exhibits bioactivities such as antineoplastic, antibacterial, and antiparasitic properties (Wasser and Weis 1999a). Moreover, the hepatoprotective and anti-inflammatory effect have been showed by schizophyllan (Wasser and Weis 1999a; Kukan *et al.* 2004; Zhang *et al.* 2013).

Medical Applications of Schizophyllan

Cancer is considered one of deadliest disease around the globe. Schizophyllan was found to control the growth of sarcoma 180 tumors (Wasser and Weis 1999b). The clinical

use of schizophyllan was approved in Japan and used as an anticancer agent due to its role in the treatment of lung and gastric cancers. Schizophyllan was also tested against neck and head cancer and results showed improved survival of patients (Kimura *et al.* 1994; Ding *et al.* 2000; Daba and Ezeronye 2003). The antitumor effect of schizophyllan is likely due to improved interferon synthesis and activation of macrophages and T-lymphocytes in the host; therefore, its anticancer effect is host-mediated (Ding *et al.* 2000). The anti-cancer agent ellagic acid was encapsulated with schizophyllan nano-particles (EA-SPG-NP) and chitin nano-particles (EA-Ch-NP). The release of ellagic acid was studied in 95% ethanol, and different mediums of digestive systems (pH: 1.5 to 7.4) before the treatment of breast cancer MCF-7 cells. The results of MTT cytotoxicity showed effective cell growth inhibition of breast cancer cell lines by EA-SPG-NP and EA-Ch-NP at IC₅₀ of 60 and 115 µg/mL, respectively (Pirzadeh-Naeni *et al.* 2020). The biological activity of schizophyllan after ultrasonic treatment was studied. Ultrasonic-treated schizophyllan (UTS) showed low molecular weight and narrow distribution. UTS fractions also caused enhancement in nitric oxide production in macrophages RAW264.7 and the proliferation rate of lymphocytes. Moreover, the level of IL-2 and TNF- α in spleen lymphocytes was also improved, while the inhibition rate of T-47D cells was enhanced. Based on the results, it was concluded that ultrasonic treatment of schizophyllan improved its anti-cancer and immune-enhancing activities (Zhong *et al.* 2015). In many types of cancers, the activation of *K-ras* mutations related to malignancy has been observed. Therefore, Sasaki *et al.* 2020 designed a complex of antisense oligonucleotide (K-AS07) and schizophyllan for silencing of *ras* gene in the PC9: human adenocarcinoma (differentiating from lung tissue) cells, expressing Dectin-1 that leads the suppression of cell growth. Moreover, the combination of antisense oligonucleotide (K-AS07)/schizophyllan complex and an anticancer drug gemcitabine improved the cytotoxic effect against cancer cells.

Schizophyllan has also been found effective as a drug delivery agent. Antisense technology could provide an effective solution for inhibition of inflammation, but it has the adverse effect of antisense nucleotide degradation by nucleases. Therefore, a suitable agent is required for delivery of antisense oligonucleotide, which improves antisense stability while retaining the specificity of antisense nucleotide for its target molecules. A system consisting of schizophyllan and antisense oligonucleotide was developed for inhibition of expression of targeted RNA or DNA. The schizophyllan complex is not dissolved in the presence of nucleases. The schizophyllan complex can be taken up easily through phagocytosis by macrophages. The macrophages produce the macrophage-inhibitory factor (MIF) that plays an important role in inflammatory bowel disease. The complex of antisense MIF and schizophyllan is capable of suppressing the synthesis of MIF (Takedatsu *et al.* 2012).

The role of dietary schizophyllan for the reduction of mitochondrial damage in liver was studied in mice. Schizophyllan showed a protective effect on liver mitochondria by inducing SIRT3, a mitochondrial NAD⁺-dependent deacetylase that results in deacetylation of succinate dehydrogenase A (SDHA) and superoxide dismutase 2 (SOD2). Mice with damaged livers caused by alcohol or conjugated linoleic acid were utilized for the analysis. The dietary supplementation with schizophyllan caused the activation of SIRT3 inhibited the damage in liver mitochondria, caused by alcohol and conjugated linoleic acid (Lee *et al.* 2020).

A biocompatible biomaterial is required for the dressing of wounds. It enhances growth of dermis and epidermis layers. Nanofibers of schizophyllan have been tested for wound dressings. A nano-fibrous scaffold of schizophyllan/polyvinyl alcohol was

generated with various weight ratios by an electrospinning technique. The electrospun of schizophyllan/polyvinyl alcohol nanofiber mats were evaluated for indirect cytotoxicity test against mouse fibroblasts (L929). The results showed no cytotoxicity for the cultivation of L929 cell. The schizophyllan/polyvinyl alcohol nanofiber mats resulted in a high performance in improving cell adhesion and proliferation with flexibility and tensile strength during cell culture. Therefore, this electrospun filament is a potential material for use in either wound dressing or skin recovery (Safae-Ardakani *et al.* 2019). Schizophyllan/silver nanoparticle composite has been prepared and characterized and found to be a potential for many biomedical applications, especially for wound healing. Triple helical schizophyllan was utilized as a reducing and stabilizing agent for silver nanoparticles preparation. The results showed that silver nanoparticles attached with schizophyllan through a strong non-covalent bond resulted in a good dispersion of silver nanoparticles within the biopolymer matrix. Schizophyllan/silver nanoparticle composite was not cytotoxic for mouse fibroblastline (NIH-313) and human keratinocyte cell line (HaCaT) (Abdel-Mohsen *et al.* 2014).

Schizophyllan has been shown effective in immunomodulatory activities, but most such studies have been performed in two-dimensional culture conditions. The immunomodulatory effect of schizophyllan in the three-dimensional microenvironment of the actual tissue might be different. Lee and Ki (2020) studied the immunomodulatory effects of ultrasonic treated schizophyllan on RAW264.7 cells encapsulated in a three-dimensional hydrogel of polyethylene glycol. The cells cultivated in 3D were less sensitive to ultrasonicated schizophyllan compared to 2D. The upregulation of M1 macrophages phenotype markers was observed by ultrasonicated schizophyllan during both conditions. Conversely, the expression of M2 macrophage phenotype markers was enhanced by ultrasonicated schizophyllan in 3D conditions that indicated induction of immune-regulation of macrophages in real tissue.

The oxidized schizophyllan (scleraldehyde) has been tested for its antimicrobial properties against Gram-positive and Gram-negative bacteria. The periodate oxidation of schizophyllan specifically cleaves the vicinal glycols in scleraldehyde to form their dialdehyde derivatives. The antimicrobial activity of scleraldehyde was determined in terms of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MIB). MIC and MIB for scleraldehyde were found in the range of 3.0 to 8.0 mg/mL. These results indicated that scleraldehyde has antibacterial activity and it can be employed as a biopreservative agent for raw hides and skin storage (Jayakumar *et al.* 2010).

Schizophyllan for Enhanced Oil Recovery

The improved recovery of petroleum oil from depleted reservoirs is an important area of research. Various techniques have been used for enhanced recovery of oil. Microbial products are considered as biodegradable and environmentally friendly for enhancement of oil recovery. Several compounds of microbial origin including biosurfactants, gases, bioacids, solvents, microbial polysaccharides, and microbial biomass are used in mobilizing the left-behind oil. The synthetic chemical used in enhanced oil recovery can be replaced by microbial products (Shoaib *et al.* 2020; Al-Ghailani *et al.* 2021). Synthetic polymers including hydrolyzed polyacrylamide and xanthan have been dominantly used for enhanced oil recovery. However, the utilization of these synthetic polymers has some limitations at high temperature and salinity reservoirs. These polymers are being hydrolysed at high temperature and are precipitated in high salt concentrations (Davison and Mentzer 1982). Schizophyllan is highly stable at high temperature due to

triple helical structure and can be used for enhanced oil recovery at high temperature. The intramolecular hydrogen bonds among helical structure provide stability to it (Al-Ghailani *et al.* 2018; Shoaib *et al.* 2020).

DIRECT ETHANOL PRODUCTION

Bioethanol production from lignocellulosic biomass is a relatively costly process due to the need of pretreatment. In addition, hydrolysis of carbohydrates and pretreatment methods also generate some substances that inhibit the ethanol fermentation. The pretreatment for lignin removal, hydrolysis of carbohydrates, and fermentation of reducing sugars are carried out in a single reactor during consolidated bioprocessing (CBP), and it has potential to lower the production cost of the final product. Some wood-degrading fungi have the ability to degrade the lignin and carbohydrates as well as ethanol fermentation ability. *S. commune* has shown the ability to produce ethanol directly from lignocellulosic biomass (Horisawa *et al.* 2015, 2019). Ethanol production from Japanese cedar (*Cryptomeria japonica*) wood using mixed culture of *S. commune* NBRC 4928, *Bjerkandera adusta* IWA5b, and *Fomitopsis palustris* NBRC 30339 was performed. During CBP, *B. adusta* IWA5b produced more ligninases under anaerobic conditions. Ethanol production during CBP using cedar wood as substrate by co-cultivation *S. commune* NBRC 4928 and *B. adusta* IWA5b was studied. *F. palustris* NBRC 30339 resulted in the production of enzymes that liberated glucose from cellulose. The co-culture of *S. commune* NBRC 4928 and *F. palustris* NBRC 30339 did not improve ethanol production, while the combination of *S. commune* NBRC 4928 and cellulase enhanced the production of ethanol significantly (Horisawa *et al.* 2015, 2019).

ENZYMES PRODUCTION FROM *S. COMMUNE*

S. commune produces several enzymes such as cellulases (Sornlake *et al.* 2017; Kumar *et al.* 2018), xylanases (Paice *et al.* 1978; Gautam *et al.* 2018), pectinases (Zhu *et al.* 2016; Mehmood *et al.* 2018), lipases (Kam *et al.* 2016), laccases (Kumar *et al.* 2015), manganese peroxidase (MnP) (Asgher *et al.* 2016), and lignin peroxidase (LiP) (Asgher *et al.* 2016), *etc.* Microbial enzymes are used in several processes in industries such as chemicals, brewery & wine, food, pulp & paper, textile & laundry, animal feed, and biofuel (Bharti *et al.* 2018; Yadav *et al.* 2018; Kumar *et al.* 2019). A variety of low cost and abundantly available lignocellulosic substrates have been used for the production of enzymes (Sornlake *et al.* 2017; Gautam *et al.* 2018). The utilization of a low-cost substrate helps to minimize the production cost of enzymes. Different agricultural residues such as corn cob, corn stover, congress grass, maize bran, wheat bran, pearl millet stover, Sabai grass, sugarcane bagasse, sugarcane leaves, rice straw, and wheat straw were tested for xylanase production by *S. commune* ARC11 under SSF. Although, rice straw resulted in maximum xylanase production (4288±143 IU/gds), other substrates were also utilized efficiently and induced fair amounts of xylanase.

Table 2. Production of Industrial Enzymes from *S. commune*

<i>S. commune</i> strain	Carbon source (substrate)	Type of fermentation	Fermentation conditions					Enzyme (yield)	References
			Initial pH	TEMP (°C)	IP (days)	IMC	Agitation		
<i>S. commune</i> ARC-11	Rice straw	SSF	7.0	30	8	70 %	-	Xylanase: 10196.53 IU/gds	(Gautam <i>et al.</i> 2018)
<i>S. commune</i> BCC23363	Avicel- PH101	SmF	-	30	7	-	200 rpm	FPase: 0.3±0.02 IU/mL Endoglucanase: 22±5.7 IU/mL Xylanase: 680±89 IU/mL β-glucosidase: 3.3±1.1 IU/mL	(Sornlake <i>et al.</i> 2017)
<i>S. commune</i> G-135 (mutant)	Avicel- PH101	SmF	-	30	7	-	200 rpm	FPase: 0.6±0.02 IU/mL, Endoglucanase: 50.8±4.8 IU/mL Xylanase: 680±89 IU/mL β-glucosidase: 3.3±1.1 IU/mL	(Sornlake <i>et al.</i> 2017)
<i>S. commune</i> SH12	Jerusalem artichoke stalk	SSF	6.5	28	5-30	1:3.3	-	Endoglucanase: 21.5±1.6 U/mg Xylanase: 112.5±2.3 U/mg Pectinase: 17.3±1.6 U/mg	(Zhu <i>et al.</i> 2016)
<i>S. commune</i> Delmar	Black spruce saw dust	SmF	3.9	30	9	-	200 rpm	Xylanase: 0.354 U/mg	(Paice <i>et al.</i> 1978)
<i>S. commune</i> NAIMCC-F-03379	Wheat bran	SmF	5.0	28	7	-	Static conditions	Endoglucanase: 36.46 IU/mL FPase: 37.01 IU/mL	(Kumar <i>et al.</i> 2018)
<i>S. commune</i> NI-07	Guaiacol or syringaldehyde	SmF	4.5	28	7	-	120 rpm	Laccase: 7307 U/mL	(Kumar <i>et al.</i> 2015)
<i>S. commune</i> IBL-06	Rice straw	SSF	5.0	35	6	66%	-	Laccase: 446.39 IU/gds LiP: 1498.1 IU/gds MnP: 1979.4 IU/gds	(Asgher <i>et al.</i> 2016)
<i>S. commune</i> BL23	Peptone, yeast extract & dextrose	SmF	6.0	35	7	-	150 rpm	Fibrinolytic activity: 4.59×10 ³ U/mg	(Pandee <i>et al.</i> 2008)
<i>S. commune</i>	Mosambi (sweet lime) fruit peels	SSF	6.0	35	1	-	-	Pectin lyase: 480.45 U/mL	(Mehmood <i>et al.</i> 2018)
<i>S. commune</i> UTARA1	Sugarcane bagasse & used cooking oil	SSF	-	30	5	1:2	-	Lipase: 0.20 U/gds	(Kam <i>et al.</i> 2016)

TEMP: Temperature, IP: Incubation period, IMC: Initial moisture content (represented either in % or in the ratio of substrate to nutrient salt solution), gds: gram dry substrate

Among all agricultural residues tested, maize bran, wheat straw, Sabai grass, sugarcane bagasse, wheat bran, sugarcane leaves, and congress grass resulted in 3962 ± 141 , 3771 ± 112 , 3681 ± 138 , 3642 ± 150 , 3587 ± 118 , 3460 ± 79 , and 3235 ± 80.89 IU/gds of xylanase activities, respectively. The results indicated that all of these agricultural residues have potential to be utilized by *S. commune* ARC11 for enzymes production (Gautam *et al.* 2018). Pandee *et al.* (2008) studied fibrinolytic enzyme production by *S. commune* BL23 under SmF, and the highest enzyme activity (576.73 U) was obtained in a peptone, yeast extract, and dextrose-containing medium after an incubation period of 7 days. *Pichia pastoris* was used for the production of feruloyl esterases that was cloned from *S. commune*. Feruloyl esterase was coded by the genes namely *fae1* and *fae2*, and these two genes were cloned in *P. pastoris* that produced 6000 U/L of extracellular feruloyl esterase (Nieter *et al.* 2016). Mosambi (sweet lime) fruit peel was used as substrate for pectin lyase production by *S. commune* under SSF. The optimization of cultural conditions was performed to achieve maximum pectin lyase production of 480.4 U/ mL (Mehmood *et al.* 2018). The production of lipase by *S. commune* UTARA1 was studied under SSF. Sugarcane bagasse was pretreated with different methods including steam, microwave, HCl, NaOH, and their combinations. The fermentation medium was supplemented used cooking oil for lipase production. Among all pretreatment tested, steam-assisted HCl pretreated sugarcane bagasse resulted in maximum lipase (0.20 U/gds) activity that was lower than that of lipase activity (0.41 U/gds) obtained from untreated sugarcane bagasse (Kam *et al.* 2016). The production of different enzymes by *S. commune* has been given in Table 2.

S. COMMUNE AND ITS ENZYMES-BASED APPLICATIONS

Lignocellulose Hydrolysis

The hydrolysis of lignocellulosic biomass is a critical step during the conversion of lignocellulosic biomass into renewable production of biofuels and value-added microbial products (Sornlake *et al.* 2017). The filamentous fungi are effective degraders of lignocellulosic biomass, and their enzymes are utilized for deconstruction of lignocellulosic biomass. Based on degradation mode, filamentous fungi can be divided into three groups, namely white-rot, brown-rot, and soft-rot. White-rot fungi (WRF) are considered one of the best producers of lignocellulolytic enzymes naturally. They are able to degrade all components of lignocellulosic biomass, *i.e.* cellulose, hemicellulose, and lignin (Yadav *et al.* 2010; Kumar *et al.* 2020). White-rot fungi play an essential role in the recycling of carbon in aerobic ecosystems. Several studies have reported lignocellulosic biomass degradation by *S. commune* (Koyani *et al.* 2014; Zhu *et al.* 2016; Sornlake *et al.* 2017). The study of genome and secretome of *S. commune* indicates that it has a large array of enzymes that can hydrolyze lignocellulosic biomass. This array of enzymes contains a variety of core and accessory hydrolytic enzymes and non-hydrolytic polysaccharide hydrolyzing enzymes. The hydrolytic enzymes are classified into different glycosyl hydrolase families. *S. commune* can also secrete different lignin-degrading enzymes with different selectivities and catalytic mechanisms working cooperatively during lignocellulose hydrolysis (Ohm *et al.* 2010; Zhu *et al.* 2016). Sornlake *et al.* (2017) evaluated the hydrolysis efficiency of lignocellulolytic system of *S. commune* G-135 that contained core and accessory glycosyl hydrolases. Lignocellulolytic system produced from Avicel-PH101 hydrolysed various lignocellulosic residues effectively. The highest

hydrolysis of 98.0% was observed from corncobs. If this enzyme was complemented with β -xylosidase, then a significant improvement was observed in xylan conversion. Zhu *et al.* (2016) compared the synthesis of extracellular enzymes of *S. commune* with other wood-decaying fungi under SSF. Results showed that *S. commune* produced significantly higher levels of hydrolytic enzymes compared to other WRF, including *Phanerochaete chrysosporium*, *Ceriporiopsis subvermispora*, and *Gloeophyllum trabeum*. The lignin modification by *S. commune* enzymes was found to be similar to hydroxyl radical attack in *G. trabeum*. The analysis of catalytic performance of *S. commune* crude enzyme extract showed higher efficiency during the hydrolysis of lignocellulosic biomass compared to commercial enzyme obtained from *Trichoderma longibrachiatum*. A higher diversity of carbohydrate hydrolyzing enzymes was observed during the analysis of extracellular enzymes produced by *S. commune* compared to the other three WRF. Furthermore, multiple non-hydrolytic proteins such as lytic polysaccharide monoxygenases and expansin-like proteins that are involved in enhancing polysaccharide accessibility were also found in *S. commune* secretomes (Zhu *et al.* 2016). The wood degradation capability of *S. commune* Fr. was analysed against wood blocks of different plants such as *Ailanthus excelsa*, *Azadirachta indica*, *Tectona grandis*, *Eucalyptus* sp., and *Leucaena leucocephala*. The results showed a smaller weight loss during the initial phase, while it became rapid after one month. The highest weight loss of 34.44% was observed for *A. excelsa* while the lowest weight loss of 24.05% was caused for wood block of *T. grandis* after 120 days of incubation. The wood blocks after fungal treatment were also analyzed for the size of pits on ray wall, creation of additional boreholes in rays, separation of fibers, and the effect of cell wall thickness (Koyani *et al.* 2014). Singh *et al.* (2021) studied the growth of *S. commune* on paddy straw, wheat straw, and saw dust at 28 ± 2 °C with moisture content of 80-90%. The mixture of paddy straw and wheat barn was found to be the most suitable substrate for the growth of fungus with maximum fresh weight yield of 91.9 gm/bag.

Feruloyl esterases of *S. commune* that was expressed in *P. pastoris* was studied for the release of ferulic acid from agro-industrial residues. The treatment of destarched wheat bran and sugar beet pectin with recombinant enzymes released ferulic acid. The feruloyl esterases treatment of coffee pulp liberated caffeic acid (>60%), ferulic acid (>80%), and p-coumaric acid (100%) after incubation time of overnight. The results indicated the applicability feruloyl esterases for the transformation of food processing wastes into valuable products (Nieter *et al.* 2016).

Pectinase for Detergent and Fruit Juice Clarification

Pectin lyase was produced by *S. commune* and applied to the apple pulp in different concentrations (1, 2, 5, and 10%) at 35 °C for 60 min. The treatment with 1% enzyme resulted in 20% enhancement in juice yield. The enzyme concentration of 2, 5, and 10% improved the juice yield by 22, 30, and 40% respectively. The compatibility of the same enzyme was also evaluated for different locally available detergent powders, and the enzyme showed maximum compatibility with Ariel followed by Surf excel (Mehmood *et al.* 2018).

Dye Degradation and Wastewater Treatment

Dyes are commonly used in textile, plastic, paper, cosmetic, food, pharmaceutical, and leather industries and released as chemical pollutant in industrial wastewater. These dyes are hazardous to the entire ecosystem, especially animals and human beings. The physio-chemical methods of dye degradation and removal have several financial and

methodological drawbacks. The bioremediation of dyes is a low cost and environmentally friendly approach. The dyes degradation and removal by *Schizophyllum commune* has been demonstrated as an effective technique (Renganathan *et al.* 2006; Asgher *et al.* 2013). The decolorization of Solar Brilliant red 80 was performed with *S. commune* IBL-06 in Kirk's basal salt medium. Initially, a decolorization efficiency of 84.8% was achieved after 7 days of treatment. After optimization of physical and nutritional parameters, 100% decolorization was achieved using maltose and ammonium sulphate as inexpensive carbon and nitrogen source respectively after 3 day of treatment (Asgher *et al.* 2013). The decoloration of xenobiotic dyes namely crystal violet, malachite green, orange G, rose bengal, and remazol brilliant blue R was studied with use of 124 strains of *S. commune*. More than 10 strains of *S. commune* showed high decoloration of malachite green, while orange G was most effectively degraded by *S. commune* strains 183, 216, and 227. The isolate 216 was found effective for the decoloration of rose bengal (van Brenk and Wösten 2021). Lignin peroxidase (1347.3 U/mL) was produced by cultivation of *S. commune* IBL-06 under solid-state fermentation using corn stover as substrate. Lignin peroxidase was purified by 5.65 folds using a pre-standardized four step procedure. The immobilization of lignin peroxidase was performed on chitosan beads and activated with gluteraldehyde. The chitosan-immobilized lignin peroxidase resulted in a highest dye decolorization of 95.45% at 30 °C. The immobilized enzyme retained 70% of activity after three repeated cycles and it was reduced to 35% after the 7th run of utilization. The immobilized lignin peroxidase was found better for dye removal compared to free lignin peroxidase (Sofia *et al.* 2016). The effect of nitrogen supplementation was studied on color and COD removal from textile effluent by *S. commune*. The results demonstrated that *S. commune* treatment removed the color by 88% in 9 days under non-sterile conditions with the supplementation of diammonium hydrogen phosphate as nitrogen source. The maximum COD removal of 85% was achieved within 8 days of treatment of non-sterile textile effluent supplemented with diammonium hydrogen phosphate by *S. commune* (Lee *et al.* 2004).

The removal of Acid Orange 7, Acid Red 18, and Reactive Black 5 by *S. commune* was studied with initial dye concentration of 10-100 mg/L. The maximum removal of azo dyes and fungal growth were observed at pH 2.0. The results showed that maximum uptake capacity for Acid Orange 7, Acid Red 18, and Reactive Black 5 was 44.23, 127.53, and 180.17 mg/g respectively by *S. commune*. The growth of fungus was inhibited on increasing the concentrations of azo dyes. The decolorization efficiency for Reactive Black 5 was higher compared to other two dyes studied (Renganathan *et al.* 2006). *S. commune* IBL-6 was exploited for biodegradation of reactive textile dye Cibacron Red FN-2BL, and results demonstrated maximum decolorization of dye in basal nutrient medium II containing 0.1% of Cibacron Red FN-2BL. This medium was supplemented with 1% of glucose, and treatment was performed for 3 days at pH 4.5 and temperature of 30 °C. The analysis of enzymatic profile involved in biodegradation showed that manganese peroxidase was mainly produced, while the activities of lignin peroxidase and laccase were minor (Bhatti *et al.* 2008).

CONCLUSION

Schizophyllum commune acts as a fungal cell-factory that is capable of producing valuable metabolites. It can grow on a low-cost substrate, *i.e.* lignocellulosic residues, to produce valuable products. The utilization of low-cost substrate minimizes the overall cost

of the final product. The enzymes produced by *S. commune* can be utilized for different industrial processes, such as biofuels production, juice clarification, dyes degradation, detergent preparation, bio-bleaching, and wastewater treatment. Schizophyllan shows diverse biological effects such as antitumor, immunomodulatory, and anti-inflammatory effects. It has also been found to improve the oil recovery.

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