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Research Article

Liquid Fermentation in Improving Functional Ingredients of *Phellinus linteus*

Ayesha Anam Zia[1], Sharoon Ejaz[2] and Xiaobin Yu[3*]
[1,3] Key Laboratory of Carbohydrate Chemistry and Biotechnology, Ministry of Education, School of Biotechnology, Jiangnan University, 1800 Li-Hu Road, Bin-Hu District, Wuxi 214122, China; [2] Key Laboratory of Industrial Biotechnology, Ministry of Education, School of Biotechnology, Jiangnan University, 1800 Li-Hu Road, Bin-Hu District, Wuxi 214122, China
ashe.butt888@gmail.com, sharoonuol@gmail.com, xbyu@jiangnan.edu.cn*; +8618626382725
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Abstract

Medicinal fungi and edible fungi are the best sources to get nutraceuticals and functional foods that have enhanced properties to use as medicinal and nutritive properties. *Phellinus linteus* is a medicinal fungus having many medicinal and nutritive effects but is very rare. There's an immense need to increase production efficiency with enhanced quality polysaccharide production derived from *Phellinus linteus*. This review mainly focuses on the production of polysaccharide and their improvement using *Phellinus linteus*. Polysaccharides and other bioactive compounds from *Phellinus linteus* mycelia help in enhancing immunomodulatory, antioxidant, anti-cancerous, anti-inflammatory, hypoglycaemic properties of bioactive compounds thus giving health and pharmaceutical benefits through liquid fermentation-based bioconversions. This review summarizes extraction, production, and fermentation conditions optimization methods used in different studies to improve many medicinal properties of polysaccharide and other bioactive compounds along with the production of products having a different mode of action in a single production process that increases the impact of using liquid fermentation for improving functional ingredients production efficiency and activity. Further studies and researches help industries in achieving nutritive benefits from *Phellinus linteus.*

Keywords: Functional components, polysaccharides, *phellinus linteus,* anti-inflammatory, anti-cancer.

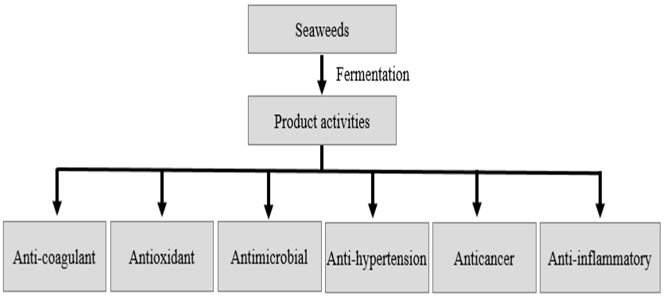
Introduction

Many of the fermentations are carried out in liquid broth despite solid culture fermentation and this kind of fermentation is known as liquid state fermentation. For the manufacturing of specific product categories and biologically active ingredients, both native and regulated fermentation was used. Fermentation enables low-cost agriculture industries to waste material to be transformed into a lot of commercial substances like enzyme production and the secondary metabolites (Krishna, 2005). Besides that, the generation of secondary metabolites through fermentation was mainly carried out by liquid fermentation on a large-scale, while solid-state fermentation remains a relatively recent method for this reason (Ruiz-Sanchez *et al.*, 2010; Sanjukta and Rai, 2016; Magro *et al.*, 2019). Owing to the natural, environmentally sustainable cycle, fermentation-derived functional ingredients are attracting interest, as well as growing market demand for good quality food (Chye *et al.*, 2018). In 2017, the market for food containing functional ingredients was at 64.75 billion USD that is estimated to reach 94.21 billion USD until 2023 due to the increasing consumption of functional food ingredients.

This increasing demand for a healthy diet is due to two factors: First is increasing awareness regarding health among consumers and second is due to the awareness consumption rate of fortified and nutritive food increased (Risvi, 2018). The main components in functional components include Carbohydrates, Carotenoids, phytochemicals, probiotics, proteins, prebiotics, omega-3 fatty acids, and plant extracts that are originated from natural or synthetic sources. These functional components are mainly a part of beverages and foods to make them functional and nutritious (Risvi, 2018). One of the most demanding food functional ingredients is seaweed products that are organic and contain valuable bioactive compounds that play a role in different biological activities shown in Fig. 1. The activities achieved after fermentation processing of seaweeds are anti-hypertension, anti-inflammatory, anti-coagulant, antioxidants (Guo *et al.*, 2003; Soong and Barlow, 2004), anti-cancer, and anti-microbial (Chye *et al.*, 2018).

*Corresponding author

Fig. 1. Different activities are performed by fermentation-derived seaweed products.



(Source: Guo *et al.*, 2003; Soong and Barlow, 2004; Chye *et al.*, 2018)

Phellinus linteus and its medicinal importance

Phellinus linteus is a name of a specie of a mushroom that belongs to the *Hymenochaetaceae* family, which is native mainly to America, East Asia, and Africa are tropical regions that mainly associated to the *Phellinus linteus* (Deng *et al.*, 2011). It is a medicinal mushroom (basidiomycete) that being used for gastroenteric dysfunction, diarrhoea, cancer, and haemorrhage as a traditional treatment for many years (Mei *et al.*, 2015). According to another study reported *P. linteus* fruiting bodies are very much expensive due to their complicated production that usually takes approximately 5 to 6 months (Lee *et al.*, 2011). Nevertheless, the advantages of the bioactive compounds of some of the mushrooms can also be extracted from mycelia directly so in this way cultivation time of these mycelia can be reduced (Hatvani and Mecs, 2001). This is a mushroom having colour range from yellow to orange and its best growth is on the mulberry tree (Kim *et al.*, 2004). *Phellinus linteus* has many medicinal benefits for using as a treatment of inflammation, stomach-aches, tumors in preventing diseases like cancers, gastroenteric disorders, and lymphatic disorders (Cho *et al.*, 2002). Many reports have presented *Phellinus linteus* against sarcoma inhibition (Chung *et al.*, 1993; Chi *et al.*, 1996; Kang et al., 1997; Han *et al.*, 1999). In 1987 for inhibiting sarcoma growth, *Phellinus linteus* fruiting body hot water extract was reported to inhibit sarcoma to 96.7% (Ikekawa *et al.*, 1968). *Phellinus linteus* has activities to boost up immunity that helps in anti-tumour activity. In China, *Phellinus linteus* has been used as traditional medicine since 2000 for treating haemostasis, female reproductive cycle associated illnesses, and haemorrhage clinically. It's also used for obesity, tumour, inflammation, diabetes, etc. imparting enhanced therapeutic efficacy (Li *et al.*, 2019). *Phellinus linteus* is a rare mushroom in nature that is insufficient to meet the medicinal benefits and market demand. For increasing its production, we should devise a proper strategy (Lee *et al.*, 2008).

Improved production of *Phellinus linteus via* Fermentation

Due to the greater number of beneficial effects, *Phellinus linteus* production is increased *via* artificial means. Among all available cultivation strategies fermentation is a highly significant technique to cultivate *Phellinus linteus* along with increasing product efficiency and decreasing drawbacks associated with it because of the addition of /improvement of functional ingredients of polysaccharides. These benefits can be achieved after optimizing mycelia growth of *Phellinus linteus via* optimizing growth conditions for fermentation (Hur, 2008; Lee *et al.*, 2011; Ding and Fan, 2012; Zhou *et al.*, 2018) as mentioned in Table 1, 2 and 3. For an increase in mycelial proliferation, dispersion, and cleavage in shaker flask water drops have been added. When we compare the nutrient level of inoculated and uninoculated cultures products as shown in Fig. 2, this depicts a high amount of increase in nutrient contents like fibre, ash, flavor, free amino acids, polysaccharides, polyols, and proteins as in the research conducted on rice and adlay cooked grains (Liang *et al.*, 2009). For increasing the growth of mycelia and biosynthesis of polysaccharides chemically defined medium, phytohormones, and physical factors play the role of a booster (Guo *et al.*, 2009a). Another study (Lee *et al.*, 2008) conducted depicts that fermentation conditions optimization is required to produce polysaccharides at a higher rate with improved morphology (Hwang, 2004; Lee *et al.*, 2008; Shu and Hsu, 2008; Guo *et al.*, 2009b; Wang *et al.*, 2014). This optimization helps in increasing mass production efficiency from uninoculated product efficiency as shown in Fig. 3. The production is enhanced due to the medicinal usage of *Phellinus linteus* derived polysaccharides (Chen *et al.*, 2016).

Importance of liquid fermentation in improving functional ingredients of *Phellinus linteus*

The growth of *P. linteus* can be successfully improved in the whey saturated wastewater, some of the benefits economically could be achieved by manufacturing effective and valuable products whereas by reducing the quantity of organic waste. Additionally, the bioconversion of the mycelium (*P. linteus*) from the wastewater could be an effective strategy for bioprocessing. Besides, bioconversion of *P. linteus* from the wastewater can be a suitable bioprocess strategy since the fungi can stand acidic pH as compared to bacteria that cannot survive in an acidic environment (Carvalho *et al.*, 2013). Though, the use of mycelia (*P. linteus*) needed for this type of process requires knowledge about physical parameters that can influence the growth of the mycelia. These growth characteristics play a major part in the development of mycelia in the medium. Two types of fermentation processes are mostly used for these types of methods, solid-state fermentation (SSF) and the other liquid-state fermentation (LSF) that has been used for many years for the cultivation of the mycelia.

*Corresponding author

Table 1. Cultivation conditions for *Phellinus linteus* growth over Mulberry (*Morus alba*) logs to obtain high yield.

Culture conditions	
Substrate	Mulberry (*Morus alba*) logs
Temperature	30°C
pH	6
Log length	20 cm
Culture media	
Carbon source	Mannose Glucose Sucrose
Nitrogen source	$NaNO_3$ KNO_3
Sterilization and inoculation duration	12 hours

Table 2. Cultivation conditions for *Phellinus linteus* growth over Cheese processing waste for increased mycelial growth.

Culture conditions	
Galactose	29.7
Temperature	26.2°C
pH	5.2
Substrate	Cheese processing waste
Mycelia growth	2.80 mm/d

Table 3. Polysaccharide production from *Phellinus linteus* by optimizing fermentation conditions of shaker flask.

Culture conditions	
Carbon source	Glucose
Nitrogen source	Soy peptone
Inoculation quantity	6%
pH	6
Temperature	28°C
Rotation speed	180 r/min
Vitamin B1 & B2	0.3 g/L
Medium volume	60%–65%
Inoculated cell age	7 days

These two techniques have many advantages and disadvantages as SSF has been used for the growth of such microorganisms that grow in the absence of water flow on a water-insoluble solid substrate medium (Liang *et al.*, 2009) and has been used to yield effective products like some of the enzymes from the mycelial substrate (Singhania *et al.*, 2009). On the other hand, submerged liquid fermentation discusses the fermentation in an aqueous media; SLF is very beneficial and associated with a greater yield of mycelia. An important benefit of SLF is that in bioprocess engineering it offers reasonable conditions for mixing. The mixes guarantee that various variables such as dissolved oxygen, optimum temperature, and proper concentration of substrate are homogeneous. In the SLF method the growth of *P. linteus* mycelium at 29°C, pH 5, and 65.3 g lactose/L in an optimum growth condition.

Fig. 2. Polysaccharide content in products produced from *Phellinus linteus* inoculated adlay and rice cooked grains were greater compared to uninoculated adlay and rice cooked grains (Source: Ding and Fan, 2012).

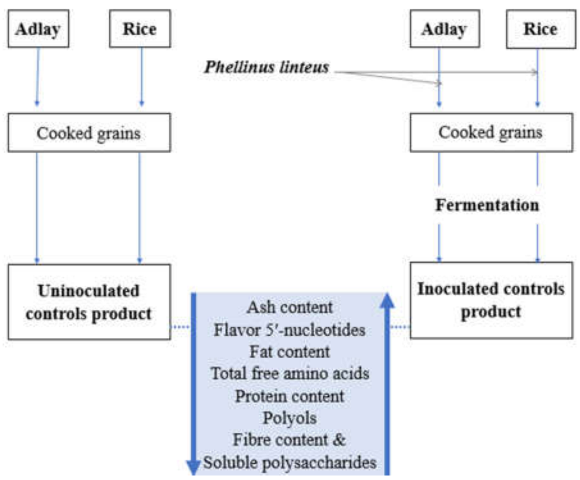
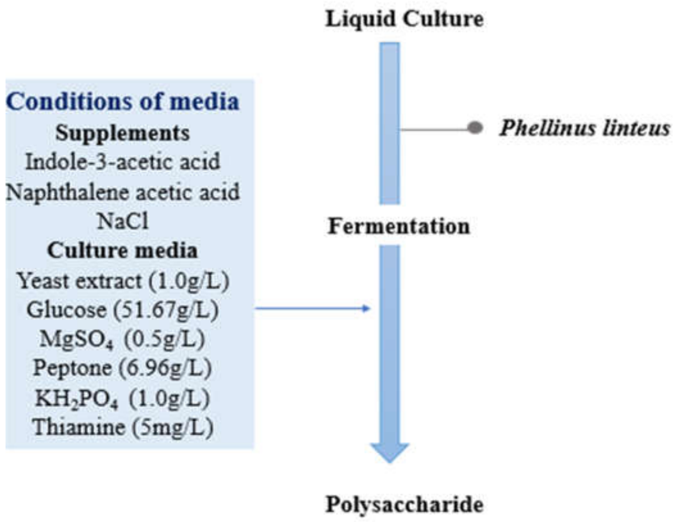


Fig. 3. Optimization of media conditions of fermentation for increasing production and morphology of *Phellinus linteus* derived polysaccharide through liquid fermentation (Source: Shu and Hsu, 2008).



The maximum growth rate in the SSF and SLF was 1.92±0.01 mm per day and 192.1±0.0 mg/L (Cho *et al.*, 2015).

Importance of *Phellinus linteus* with broth culture

Phellinus linteus has a beneficial role that includes maintaining blood glucose level, improves the circulation of blood, and improving the immunological properties. *Phellinus linteus* was shown to have anti-tumour, anti-inflammatory, antioxidant, anti-hyperlipidaemic, anti-diabetic and immunomodulatory activities.

*Corresponding author

While *P. linteus* is an outstanding medicinal mushroom and commonly used in East Asia with a range of bioactivities, wild *P. linteus* resources are scarce and limited in size which supports artificial culture for better development. As a result, *P. linteus* fermentation plays a major role in promoting exploitation and use. Several recent studied to improve conditions to define suitable physicochemical properties for mycelial growth parameters that were performed to satisfy specific needs and requirements (Chen *et al.,* 2016). Using chromatographic techniques, another study reported that the chemical constituents of liquid cultures and *P. linteus* mycelium (Wu *et al.,* 2010).

Phellinus linteus as a potential therapeutic agent against skin pigmentation

A mycelial culture broth of 8 forms of herbal extracts, fermented by *Phellinus Linteus* (previously identified as 8-HsPLCB), not just blocked melanin production and activity of tyrosinosis, but decreased the contents of proteins linked to melanogenesis in the 3-isobutyl-1-methylxanthine-stimulated B16F0 melanoma cells, including tyrosinases and microphthalmia-associating transcription factor. Furthermore, the 8-HsPLCB effect reported against pigmentation of the skin with ultraviolet B (UVB)-tempted hyperpigmentation in brown guinea pigs. The finding from these studies assumes that the *Phellinus linteus* role in skin lightening may be the result of melanin synthesis inhibition *via* tyrosinase within melanocytes. Finally, 8-HsPLCB therapy demonstrated melanin pigment reduction and histological improvements in brown guinea pigs as a result of UV irradiation (Ahn *et al.,* 2018).

Induction of potential anti-inflammatory effect _via_ _Phellinus linteus:_ In macrophages, *P. linteus* and its component hispolon induce the strong anti-inflammatory effect. In controlling innate sensing, effective manufacturing of the appropriate constituent and the biological activity of *P. linteus* was rarely studied. The major goal of this study was to produce fermented broth of *P. linteus* that contains active components, hispolon, and the other aim was the evaluation of immunoregulatory activities in the macrophages. The screening of the appropriate culture conditions for the growth of *P. linteus* mycelia included four different fermented broths (PL1-4) and medium dialysate (MD). The fermented broth of *P. linteus* showed a dose-reacting lipopolysaccharide (LPS)-induced nitric oxide (NO) inhibition caused by the production of murine macrophages. Also, macrophages LPS mediated-nuclear factor (NF)-kB activity and tumour necrosis factor (TNF)-α were inhibited by the *P. linteus*-fermented broths. Even amongst the tested samples, PL4 constituted large amounts of hispolon in both RAW264.7 cells and murine primary peritoneal exudate macrophages (PEM), which showed the highest anti-inflammatory activity. This study concludes that effective components from the fermented broth of *P. linteus* mycelia aid in the development of potential therapeutic agents This study demonstrates that the purification of the effective constituent from *P. linteus*-fermented broth may enable the production of a potent therapeutic agent in macrophages for anti-inflammation (Lin *et al.,* 2014). We have noticed that the *P. linteus* fermentation broth has a good inhibitor of neuraminidase throughout our search for neuraminidase inhibitors extracted through medicinal fungi. Two active agents were isolated from the ethyl-acetate-soluble part of the *P. linteus* fermentation broth by bioassay-directed fractionation. The structures were then identified by spectroscopic methods as follows (i) inotilone and (ii) 4-(3,4-dihydroxyphenyl)-3-buten-2-one. The two compounds exhibited a role in the inhibition of the activity of H1N1 neuraminidase followed by Dose-dependent IC50 values of both 29.1 and 125.6 µM. In an MDCK (Madin–Darby canine kidney) viral cytopathic effect reduction test they have also shown an antiviral effect. The results indicate that the above written (i) and (ii) compounds 1 and 2 from *P. linteus* culture broth are ideal candidates for viral infection prevention and therapeutic strategies (Hwang *et al.,* 2014).

Phellinus linteus mechanism and respective biological activities: The biological activities of *P. linteus* and their mechanism involved are discussed in Table 4. In which *P. linteus* perform various mechanisms based on its biological activities that either improve the production of some components or reduce their production are listed.

Role of Liquid fermentation in improving bioactive compounds in _Phellinus linteus_ with its functional significance: *Phellinus linteus* has been shown as an important therapeutic agent in Chinese traditional medicine for the prevention and treatment of many diseases and a significant source of the certain bioactive element, such as furans, polysaccharides, ergosterols, glucans, triterpenoids, and phenylpropanoids as shown in Fig. 4 (Lee *et al.,* 2014; Reis *et al.,* 2014; Taofiq *et al.,* 2016). Ethanolic extract, methanolic extracts, glucans, triterpenoids, and polysaccharides were tested with the bioactivity of *P. linteus* (Chen *et al.,* 2019). Methanolic extract provided the strongest antioxidant and antibacterial activities, while glucan and triterpenoid fractions were most efficient. Ethanolic extract, in comparison, yielded the highest performance in cytotoxic activity and showed the synergistic effect of bioactive compounds. There are different components of these bioactive compounds playing a role in different disease prevention as mentioned in Fig. 5 and Fig. 6 (Chen *et al.,* 2019). These compounds production capacity is limited which is enhanced by liquid fermentation which also increases the purity of released bioactive compound along with functional improvement.

*Corresponding author

Table 4. Biological activities and mechanisms of *P. linteus.*

Biological activities	Mechanism
Immunomodulatory	Improved B and Tcell proliferation, Protein tyrosine kinase, decreased cytokines production like IL-4 & IFN-g
Anti-oxidative	Decrease the production of ROS (reactive oxygen species) & free radicals and improve the production of superoxide dismutase, catalase & glutathione
Anti-microbial	Exhibit potent activities against *Porphyromonas gingivalis* & MRSA and the decreased activity of enoyl-ACP reductase.
Anti-viral	Exhibited antiviral effect against H1NI, H5N1, A/WS/33 from influenza
Anti-inflammatory	Improved IL-10, IL-4 & suppressed IL-1 beta, IL-2, IL-6, TNF alpha, and some catalases

Fig. 4. Production of bioactive compounds from *P. linteus* through liquid fermentation (Source: Lee *et al.*, 2014; Reis *et al.*, 2014; Taofiq *et al.*, 2016).

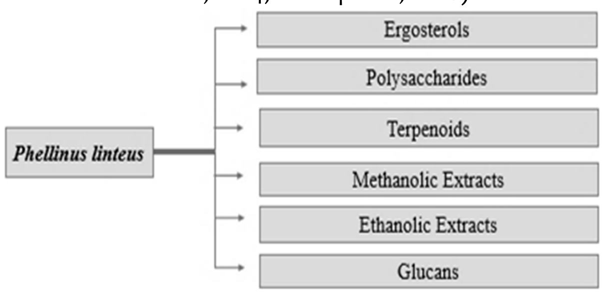


Fig. 5. Fermentation based production of phenylpropanoid (bioactive compounds) from mycelium and fruiting bodies of *P. linteus*. The functional significance of components in phenylpropanoid (Source: Chen *et al.*, 2019).

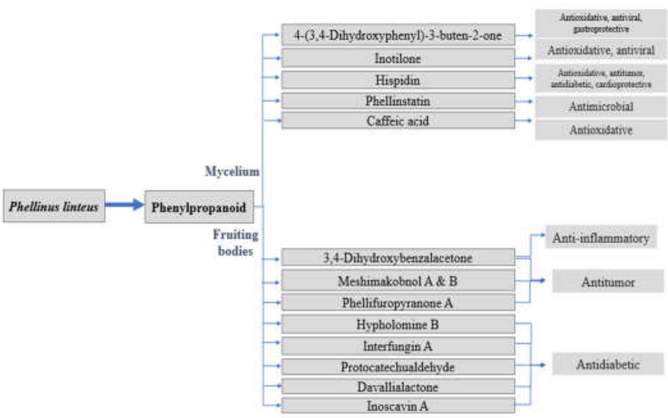
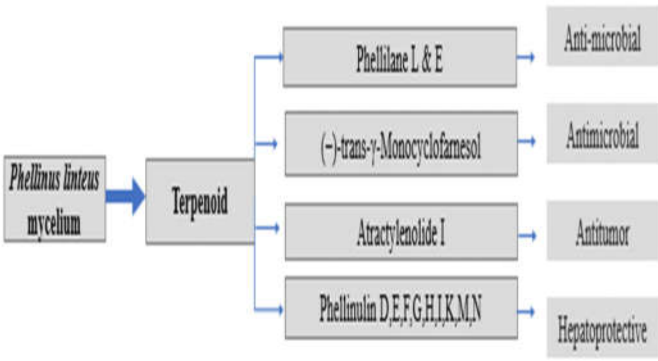


Fig. 6. Fermentation based production of terpenoids (bioactive compounds) from mycelium with the functional significance of components in terpenoids (Source: Chen *et al.*, 2019).



However, the most abundant and potent mushroom-based substances with anti-tumorous and immunomodulatory properties are, promote humoral and cell-based immunity. Polysaccharides (especially β-D-glucans and polysaccharide-peptides (PSP)), the biological functions of the triterpenoids are also important. There are some propanoid like phenyl propanoid released from *Phellinus linteus* as shown in Fig. 5. These phenylpropanoid have many components some released from mycelium and some from fruiting bodies of *Phellinus linteus*. These components have different biological significance as shown in Fig. 5. The triterpenoids antitumor and immunomodulatory effects increasingly intensify the interest in biochemical and medical fields as shown in Fig. 6 mycelia of *Phellinus linteus* produces terpenoid that has compounds shown in Fig. 6 play role in different biological activities.

Role of *Phellinus linteus*-derived polysaccharides in therapeutics: Polysaccharide produced from *Phellinus linteus* associated with many activities like anti-angiogenic (Song *et al.*, 2003), humoral and cell-mediated immunity (Song *et al.*, 1995; Kim *et al.*, 1996; Berovic *et al.*, 2003), antioxidant activity (Song *et al.*, 2003), protein kinase C activation, and protein tyrosine kinase activation (Kim *et al.*, 2003). Due to these benefits, the quality, activity, and production of *Phellinus linteus* is enhanced by liquid fermentation (Zhong and Tang, 2004) (Berovic *et al.*, 2003; Hwang *et al.*, 2003) by optimizing conditions. This review highlights all possible ways to increase product quality and activity of polysaccharide derived from *Phellinus linteus* enlisted in different researches (Lee *et al.*, 2008; Zhong and Tang, 2004). Liquid fermentation of *Phellinus linteus* helps in the production of polysaccharide from mycelia that exhibit anti-cancerous activity as well as increased the yield of producing polysaccharide by optimizing media condition as shown in Fig. 7 (Lee *et al.*, 2008).

*Corresponding author

Fig. 7. Anti-cancerous activity and production of polysaccharide extracted from *Phellinus linteus* is enhanced by liquid fermentation under optimized cultural conditions (Source: Lee *et al.*, 2008).

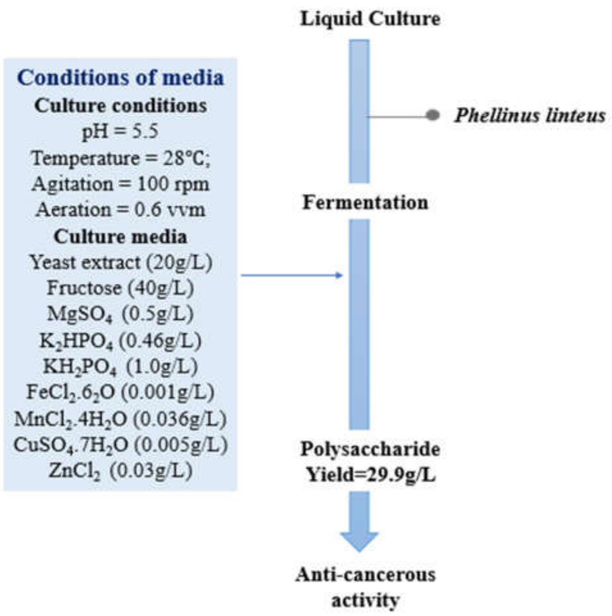
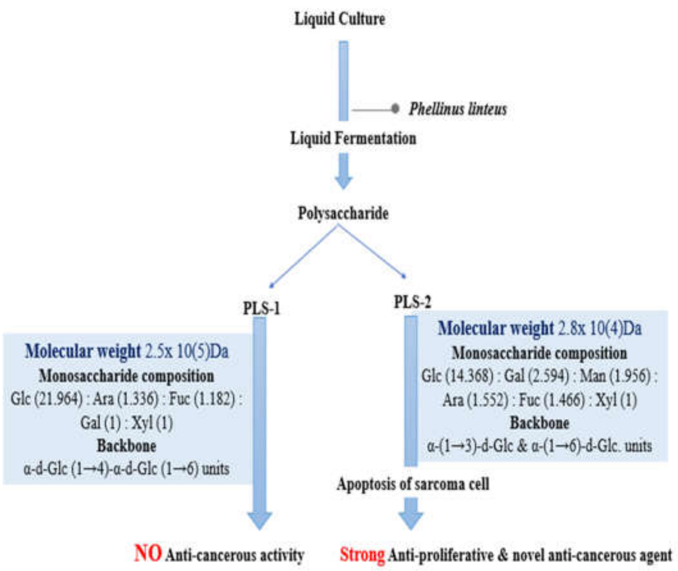


Fig. 8. PLS-2 polysaccharide produced via *Phellinus linteus* differs from PSL-1 in molecular weight, composition, backbone resulting in the difference in functionality. PSL-2 exhibits strong anti-proliferative activity and a novel anti-cancerous agent by sarcoma cell apoptotic activity while PSL-1 is unable to exhibit such activity (Source: Mei *et al.*, 2015).



Phellinus linteus derived polysaccharides improvement based on biological activities: There are different polysaccharides isolated from the same culture having different functional properties based on their structural difference as shown in Fig. 8 for PLPS (Phellinus linteus mycelia derived polysaccharide)-1 and PSPL (Phellinus linteus mycelia derived polysaccharide)-2 produced by fermenting cultures with *Phellinus linteus* (Mei *et al.*, 2015). Oral glucose tolerance test (OGTT) by administering 100 mg/kg body weight/d of PLP-1 to alloxan-induced diabetic mice revealed its hypoglycaemic properties and its usage as an additive of functional food due to their hypoglycaemic effect. PLP-1 and PLP-2 purification is catalyzed by chromatography (Sephadex G-100/ Sephadex A-50) and structural confirmation studies by nuclear magnetic resonance spectroscopy and Fourier transform infrared spectroscopy (Shahbaz, 2020; Zhao *et al.*, 2014). Myocardial ischemic-reperfusion (IR) injury associated mortality and morbidity are increasing worldwide. *Phellinus linteus*-derived polysaccharide *via* liquid fermentation help in reducing mortality and ventricular arrhythmia by reducing the level of plasma lactate dehydrogenase and the size of infarct results from myocardial injury when studied in myocardial infraction subjected rats. This reduction is due to the activity of *Phellinus linteus* polysaccharide on AMP-activated protein kinase (AMPK) pathway stimulation by enhancing AMPK phosphorylation level, beclin-1-dependent pathway inhibition via decreasing Beclin-1 and p62 level, regulating autophagy signalling via reducing mammalian target of rapamycin (mTOR), caspase 9 & 3 activation and increasing Bcl-2/Bax signalling. All these pathways ultimately lead to suppress pro-apoptotic and regulate autophagic signaling (Su *et al.*, 2017).

Phellinus linteus derived polysaccharide also helps in decreasing tumour necrosis factor α (TNF-α) by liquid fermentation production of polysaccharide under optimized conditions. This study confirms immune-suppressive activity on RAW 264.7 cells. Along with decreasing TNF-α it also increases IL-10 activity decreasing IL-6 transcription to restore IL-10/IL-6 balance to protect the body against depression, obesity, mania, chronic inflammatory diseases, diabetes type 2. Due to all these beneficial effects, it's used for the medicinal purpose (Hwang *et al.*, 2003; Suabjakyong *et al.*, 2015). Polysaccharide produced from *Phellinus linteus* mycelia through liquid fermentation helps in regulating gut-associated microbiota due to the hypoglycemic activity of *Phellinus linteus* polysaccharide extract (PSPE) in diabetic patients. It is also used as a prebiotic to regulate beneficial microbial growth in the gut (Liu *et al.*, 2020; Shahbaz and Yu, 2020).

*Corresponding author

Conclusion

Different cultures are used in different studies for increasing the nutrient-value of bioactive compounds through liquid fermentation. *Phellinus linteus* is one of the cultures giving many medical and health benefits when used on the different substrate *via* liquid fermentation. The *Phellinus linteus* mediated conversion *via* liquid fermentation increase bioactive compounds of the waste being processed to be used as a substrate for it. Due to the widespread applications of *P. linteus*, there is an immense need to include biomedical and therapeutic strategies utilizing liquid fermentation as a bioconversion tool. Further study and researches should elaborate on the functional ingredients of mycelia *P. linteus* and focuses on the production of polysaccharides as different polysaccharides produced from the same culture containing different functional properties. *P. linteus* derived polysaccharides improve the yield by optimizing different culture conditions. The focus of this review is on *Phellinus linteus* derived polysaccharide due to its wide applications in pharmaceuticals and health associated benefits. More researches will increase product efficacy by using improved techniques and parameters that give benefit to industries, pharmaceuticals, and health.

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*Corresponding author