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Review

Beyond Enzyme Production: Solid State Fermentation (SSF) as an Alternative Approach to Produce Antioxidant Polysaccharides

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Abstract: Solid state fermentation (SSF) is a sustainable process that uses low amounts of water and transforms plant-based agro-industrial residues into valuable products such as enzymes, biofuels, nanoparticles and other bioactive compounds. Many fungal species can be used in SSF because of their low requirements of water, O_2 and light. During SSF, plant-based wastes rich in soluble and insoluble fiber are utilized by lignocellulolytic fungi that have enzymes such as lignases, celullases or hemicelullases that break fiber hard structure. During the hydrolysis of lignin, some phenolic compounds are released but fungi also synthetize bioactive compounds such as mycophenolic acid, dicerandrol C, phenylacetates, anthraquinones, benzofurans and alkenyl phenols that have health beneficial effects such as antitumoral, antimicrobial, antioxidant and antiviral activities. Another important group of compounds synthetized by fungi during SSF are polysaccharides that also have important health promoting properties. Polysaccharides have antioxidant, antiproliferative and immunomodulatory activities as well as prebiotic effects. Fungal SSF has also proved to be a process which can release high contents of phenolics and it also increases the bioactivity of these compounds.

Keywords: solid state fermentation; phenolic compounds; enzymes; polysaccharides

1. Introduction

The innovation implied in the idea of turning food waste into valuable chemicals, which are used daily in human activities, is commercially attractive and involves further research in areas such as biotechnology, nanotechnology, food science and food technology [1]. There is an enormous demand for food and energy to fulfill the requirements of the increasing population and since food waste is growing too, the need of effective waste management strategies and procedures is urging as rapid urbanization continues in many countries [2]. The accumulation of food waste corresponds to 1/3 of the world's total food production [3]. Currently, most countries are focused on the prevention of food waste and little is done to convert food and organic wastes and residues into new value-added products. Therefore, as food waste processes are not implemented, their potential value is overlooked.

Solid residues from agricultural industries as well as vegetable waste are potential sources of important substances that could be employed in the chemical, food, pharmaceutical and cosmetic industry. Through recent studies of food supply chain, it has been found that useful products, such as enzymes, biofuels, biodegradable plastics, nanoparticles and bioactive compounds, among others, can be obtained [2]. Among the valuable compounds that can be obtained from organic waste, polyphenols are the most abundant, as they are found in vegetables, cereals, beverages and fruits. These substances are the ones that give color and other important organoleptic features to food, in addition to many

different beneficial effects on health to prevent or treat chronic diseases [4]. Among the several technologies used to obtain valuable compounds from organic waste, solid state fermentation (SSF) is perhaps the most promising one because of its economic and sustainable characteristics: product yielding, high efficiency and productivity, low consumption of energy and water and minimum concerns about solving disposal problems [1].

2. Solid State Fermentation (SSF)

Solid-state fermentation (SSF) is a fermentation process where microorganisms are able to grow in a low water environment [5]. This process is performed using microorganisms growing on moist and solid substrates that have been used for thousands of years to produce foods such as bread and cheese.

The most important aspect to consider while developing the SSF process is the choice of microorganisms and substrates. Fungi and mold are employed for SSF because they need less energy for substrate sterilization and are less susceptible to bacterial contamination. Filamentous fungi are particularly appropriate for SSF because this method simulates their natural habitat. This type of fungi is capable of synthesizing large quantities of enzymes and other metabolites under SSF conditions. Yeasts and some species of bacteria (e.g., *Bacillus subtilis*, *Bacillus thuringiensis* and *Lactobacillus* sp.) are considered as the second-best choice because of their ability to flourish in environments with low water activity. *Streptomyces* sp. and other *Actinomycetes* can also be employed in SSF because of their resistance to extreme conditions and capacity to colonize solid residues abundantly [6].

The most common substrate utilized in SSF are plant cultivation and forestry remains because they are underutilized and plentiful. All these wastes are comprised by cellulose, hemicellulose, starch, pectin, lignin and other fibers. Sugarcane bagasse, cassava bagasse, corn cobs, wheat bran and other cereal brans, fruit peels and pulps, coffee pulp and husks, straws and husks from distinct sources are the most frequent agro-residues used for SSF as substrates [6,7].

Most agro-industrial residues (such as residues from fruits, corn, paddy and wheat) can be changed through the use of SSF to enrich their antioxidant properties for different uses, such as animal feed [6]. Ligninolytic exoenzymes, which are produced during SSF, break the chemical links of lignin by depolymerizing the complete structure toward simpler ones. SSF can be used to obtain bioactive compounds since enzymes produced by microorganisms (such as esterases, amylase, cellulases and xylanases) release bound phenolic compounds [7]. Among the positive aspects of SSF are: no need of organic solvents to extract the released phenolic compounds; greater quality and activity of extracts; operating and capital costs are lower, etc. In the same way, SSF yields superior enzymatic productivity for numerous enzymes, it has less susceptibility to substrate hampering, and therefore, it produces a greater final concentration of desired metabolites [6]. SSF has a lot of potential to boost the extraction yield of bioactive substances that may be recovered by emerging technologies, such as ultrasound, pulsed electric fields or microwave, which have been already tested in products such as potato peels [8].

Although SSF is not a novel technology, recently, it has become a very relevant process for the production of pharmaceutical, biochemical and food products, as well as for bioenergy generation. The products obtained enable greater enzymatic productivity for numerous enzymes because they are less prone to substrate inhibition [1]. Other applications of SSF include: pigments, aroma and/or phenolic compound production, composting, biobleaching, etc. [6]. Remnants of SSF (which have a different level of biodegradability) can be used for composting, anaerobic digestion or to produce biogas [1].

3. Phenolic Compounds in Fungi

Phenolic substances are secondary metabolites generated mostly by plants. The biosynthesis of phenolic acids begins with phenylalanine, which is the first substrate during the phenylpropanoid route [9]. Phenolics can enter the organs through the transporter protein penetrating the compartment membrane [10]. Phenolic acids content is largely influenced by factors such as agronomic practices and environmental conditions, as well as different abiotic and biotic stimuli. Genetics influence phenolic

acids content too because of the environmental interactions that cause a sizeable discrepancy among species and cultivars of the same species [9].

Intracellular organs (such as the endoplasmic reticulum) synthesize phenolics and later these compounds are liberated and moved into the matrix of the cell or the vacuole through a small lipid bilayer system (vesicle transfer system). This system can hold phenolics and it also makes their migration easier into the matrix of the cell wall. It has been observed that the cytoplasmic and Golgi vesicles that contain phenolics move to the plasma membrane and secrete phenolics to the cell wall matrix. Additionally, the phenolic compounds can reach the cell wall matrix as they are moved to the plasma membrane via ATP-binding cassette (ABC) transporters [10]. The phenolic compounds that were transferred are found now linked to bigger molecules (for examle, cellulose, pectin and proteins) by covalent links (such as carbon-carbon, ether and ester) [11].

Phenolic compounds are found inside the matrix of plants in three ways: free, soluble-bound (conjugated) or in insoluble-found form. Conjugated phenolics are found esterified to soluble compounds like some low molecular weight carbohydrates, proteins or lipids, while insoluble are esterified or etherified to more complex cell wall components [12]. Bound or insolvable phenolics are also called non-extractable phenolics and stay in the matrix of the biowaste after the removal process of solvable phenolics using a water-alcohol solution [13]. Phenolic non-soluble compounds are found in cell wall matrix of the vegetable cells. They can only be liberated from the matrix by a process of hydrolysis (such as acid, alkaline or enzyme hydrolysis) [10].

Since phenolic compounds have a protecting function in plants, they also should be deemed vital for the survival of endophytic fungus or at least for their mutually beneficial relationships. However, it is not clear yet if phenolic compounds have the same importance for plants than for their connected microorganisms [14].

3.1. Biosynthesis of Phenolic Compounds in Fungi

It has been reported that occasionally the phenolic compounds initially biosynthesized by vegetables may be found in endophytes fungi colonies. Among these compounds are: emodin, capsaicin, luteolin, hypericin and chlorogenic acid [14]. In fungal endophytes, flavonoids, phenolics and saponins are very important bioactive constituents which are considered as innovative and feasible antioxidant supplies. For example, natural antioxidant compounds such as phlorizin, rutin, gallic acid and 2,6-di-tert-butyl hydroquinone were identified in fungal filtrates from 53 different endophytes from the fermented bulbs of *Fritillaria unibacteata* var. *wabuensis* (FUW), and all of these compounds showed antioxidant activities [15].

In fungi, the Shikimate pathway has been correlated with the presence of phenolic compounds in these microorganisms. Tyrosol, a well-known phenolic compound, has been isolated from extracts of endophytes from the fermentation of various plants and it is thought to be a signaling substance in fungi species [14]. Bioactive properties of other phenolic compounds from fungi include antitumor, antimicrobial and antioxidant activities (Table 1). The interaction between the substrate and the fungi affects the production of bioactive metabolites [16]. For example, when *Stemphylium globuliferum* grew in solid white bean medium, it produced tetrahydroanthraquinones that were inactive against the L5178Y mouse lymphoma cell line, but when it was grown in a rice culture, other anthraquinones that inhibit the growth of the lymphoma cells were produced [17].

Ampelomyces sp., is an endophytic fungus which can synthetize several phenolic secondary compounds through solid and liquid fermentation. Some of the phenolic compounds produced by this microorganism are: mycofenolic acid, dicerandrol C, cytosporone C, phomopsin A, phomopsin B, altersolanol A, desmethyldiaportinol, etc. These two last compounds demonstrated favorable cytotoxic activity in vitro against L5178Y mouse lymphoma cell lines; other phenolics produced have antimicrobial action against *S. aureus*, *S. epidermidis* and *E. faecalis* employing minimum inhibitory concentration values between 12.5–25 µg/mL. *Pestalotiopsis* sp. and *Phoma pinodella* can produce phenolics such as phomodione, usnic acid, cercosporamide, pestalol D and E and several others, some

of which have antiproliferative action against a group of human tumoral cell lines (such as lung, prostate, ovary, colon, cervix, etc.) [14].

Table 1. Bioactivity of phenolic compounds synthetized by fungi.

Phenolic Compounds	Reported Bioactivities	References
Mycophenolic acid: (caproate)	Immunosuppression for kidney transplant recipients	[18]
Dicerandrol C (xanthone)	Antimicrobial actions against *S. aureus*	[19,20]
Cytosporone B and C (phenylacetates)	Inhibitory action against *C. albicans* and *Fusarium oxysporum*	[20]
Phomopsin A and B (mycotoxins)	In vitro activity against *B. megaterium* and *E. coli*	[21]
Altersolanol A, B and N (anthraquinone)	Cytotoxic action in vitro against L5178Y mouse lymphoma cell lines and antimicrobial activity against *S. aureus, S. epidermidis* and *E. faecalis*.	[22,23]
4-dehydroaltersolanol A (anthraquinone)	Cytotoxicity against L5178 mouse lymphoma cells.	[24,25]
Dihydroaltersolanol C and acetylalterporriol E (anthraquinones)	Strong cytotoxicity against the murine lymphoma cell line L5178Y.	[26]
Alterporriol T	Inhibition of alpha-glucosidase	[26]
Nigbeauvin A and B (azaphilones)	Cytotoxic against tumor cells HL-60, A-549, SMMC-7721, SW480 and MCF-7.	[27]
Phomaether A and C anthraquinones)	Strong inhibitory action against *S. albus*, *S. aureus*, *E. coli* and *V. parahaemolyticus*.	[28]
Desmethyldiaportinol (isocoumarine)	Antagonist activity in vitro against L5178Y mouse lymphoma cell lines.	[25]
Phomodione (benzofuran)	Antagonist effect against *S. aureus*, *Pythium ultimum*, *Sclerotinia sclerotiorum* and *Rhizoctonium solani*	[25]
Usnic acid (benzofuran)	Activity against *S. aureus*, *Acinetobacter baumannii* and *Klebsiella pneumonia* and anti-inflammatory activity	[25]
Cercosporamide (benzofuran)	Mnk inhibitory activity via the blockage of eIF4E phosphorylation. Anti-cancer effects in hepatic and lung cancer, leukemia and glioblastoma	[29,30]
Pestalol D (alkenyl phenol)	Inhibitory activity against Influenza A virus subtype (H_3N_2) and Swine Flue (H_1N_1) viruses.	[31,32]

3.2. Phenols Release from Vegetable Cell Walls Using Fungi

Microorganisms have limited accessibility to cellulose and hemicellulose in plant cell walls due to chemical connection with lignin. Fungi are the main microorganisms that recycle cellulose in nature; these organisms are well-fitted for the decomposition of biomass from plant waste because they produce an elevated number of enzymes of wide diversity and with several supportive functions. Lignocellulosic compounds involve three major groups of polymers: cellulose (linear polymer of b 1–4 of glucose bonds), hemicellulose (polymers non-cellulosic, which include glucans, mannans, arabinans, galactans and xylans) and lignin (complex polyphenol) [33].

Lignin is a network made by phenolic compounds and it is commonly found in secondary cell walls, especially in woody tissues. It provides structure and rigidity to cells and its proportion increases with maturation. It can be found embedded in cell walls between cellulose and hemicelluloses and its concentration depends upon cell type, stage of maturation and plant species. Lignin is synthesized in the secondary wall formation and it is found throughout the cell wall of plants [34]. Lignin contains about 40 oxygen-linked phenyl-propane elements and it is chemically inactive. Ferulic and coumaric acids are some of the most studied phenolic acids because of their abundance in plants. These compounds give rigidity to cell walls because they crosslink the sugar moieties and also lignin [12].

Fungi degrade first lignin through the effect of lignolytic enzymes (lignin peroxidase, manganese peroxidase and laccase) and then can access energy-rich polysaccharides for their metabolism and growth [5]. Enzymatic hydrolysis of phenolic conjugates not only release free phenolics but also produce lower molecular weight that contribute to increase the antioxidant activity [35]. In fruits and vegetables, phenolic compounds can be released from pectins and cellulose using enzymes such as beta-glucosidase [33].

3.2.1. Fungal Enzymes for Cellulose Degradation

Three matching enzymatic effects have been suggested to be accountable for cellulose decay: β-glucosidases (GH), endoglucanases (EG) and cellobiohydrolases (CBH). These enzymes can hydrolyze the β-1,4 covalent connections that attach the glucose units present in cellulose chains. β-glucosidases are non-processive enzymes due to their substrate: it must be liberated after each split activity to let the novel glucose unit to exit the compartment. Endo-1,4-β-D-glucanases, EC 3.2.1.1 arbitrarily slice β-1,4 bonds in cellulose amorphous regions; these enzymes generate different reducing and non-reducing sides with this activity. Endoglucanases, as well as β-glucosidases, are firmly hampered by their reaction compounds: cellobiose and glucose correspondingly. Cellobiohydrolases (such as cellulose 1,4-β-cellobiosidases and EC 3.2.191) are processive enzymes that liberate cellobiose (i.e., two units of glucose linked by a β-1,4 bond) from reducing or non-reducing edges from cellulose sections obtained from endoglucanases [36].

Different fungi have been used for the production of cellulases, including *Aspergillus terreus*, *Trichoderma reesei*, *Aspergillus niger*, *Trichoderma asperellum*, *Pleurotus ostreatus* and *Aspergillus oryzae*. Fungi such as *Rhizomucor miehei* and *Aspergillus niger* produce enzymes such as cellulases and pectinases that break the cellulosic chains to obtain bioenergy from the residues [37]. The activity of these enzymes may be affected by their absorption into the lignocellulosic matrix used as substrate. This gives an additional advantage to SSF since end products may be obtained without the need of using pure enzymes [38].

Aerobic fungi have multiple enzymes that are mostly active with cellulose: lytic polysaccharide monooxygenases (LPMOs) can perform copper-mediated oxidative splitting of cellulose and AA9 enzymes can act on xylan and xyloglucan. Additionally, expansins (non-catalytic proteins) are thought to have a role in cellulose degradation (reduction of substrate viscosity as well as disruption of cellulose fibers were observed sometimes), but their mechanism has not been totally clarified because no hydrolytic activity was reported [36].

3.2.2. Fungal Enzymes to Release Phenolic Compounds

Ligninases are a large group of intricate enzymes (for example, peroxidases and laccases) that collaborate to break down the phenolic compounds from lignin. These enzymes cleave the carbon-carbon and carbon-oxygen bonds that hold in place the complex three-dimensional (3D) structure of lignin. Some sorts of ligninases are a class of copper enzymes (known as laccases), and other three kinds are peroxidases-lignin peroxidases, manganese peroxidases and flexible peroxidases. There is a robust synergy among all these types of enzymes and it is considered as one of the likely outstanding utilizations for lignin appreciation [36].

Lignocellulolytic fungi are very common in the fungal kingdom. Simple and primitive fungal species such as *Chytridiomycetes* up to more complex and advanced ones (such as Basidiomycetes) degrade cellulose very efficiently as they use it as a carbon supply. Fungi prefer to decompose lignin, cellulose and hemicellulose (e.g., white rot fungi) but also decompose polysaccharides and alter lignin (e.g., brown rot fungi); or may rot lignin and polysaccharides at the same time (e.g., soft rot fungi). This kind of fungi produce enzymes that, either independently or as a conglomerate, break and digest recalcitrant lignocellulose [36].

Table 2 shows the chemical and bioactive effects of secondary metabolites obtained through enzymatic fermentation. In general, enzymes increase the extraction yield of secondary metabolites due to their release from complex substrates. The substrates utilized to recover bioactive metabolites were mainly food and plant-based wastes which commonly have no further use. By using enzymes, synthetized from microorganisms or bought from commercial brands, most of the metabolites display good bioactive effects. Additionally, the energy employed during the process is lower than in traditional extraction methods (such as acid or heat extraction).

Table 2. Utilization of enzymes to obtain secondary metabolites from cellulosic materials.

Food/Substrate	Enzyme	Chemical Effects	Bioactive Effects	Reference
Sweet potato (*Ipomoea batatas* (L.))	Feruloyl esterases from *L. acidophilus*	The pH values of sweet potato fell from 6.2 to 3.45. Higher contents of free ferulic acid and p-coumaric acid.	Higher inhibitory effects on pheochromocytoma-cancer-cell proliferation.	[39]
Spent espresso grounds (SEGs)	Cellulase and hemicellulase	A maximum reducing sugar yield. Flavonoids and polyphenols increased by 24.0% and 33.9%, respectively.	2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) free-radical scavenging activity increased by 59.9%	[40]
Oats (*Avena sativa* L.)	α-amylase and xylanase produced by *Monascus anka* in solid state fermentation.	The phenolic content increased significantly, especially the ferulic acid in the insoluble fraction and the vanillic acid in the soluble portion.		[41]
Rice bran	Carbohydrases (Viscozyme, Termamyl, Celluclast, AMG, Ultraflo and Pentopan)	Increased the amount of extractable phenolic acids by 2.5–3.0 times.	Significant increase in ferric reducing effect (1.5–3.3 times).	[42]
Steamed rice bran	alpha-amylase, complex enzymes obtained from lactic acid bacteria.	Enhanced the whole phenolics and flavonoids of aqueous solutions from rice bran pretreated with α-amylase.	The antioxidant action of aqueous solutions also increased after the process.	[43]
Black grape (*Vitis vinifera* x (*Vitis labrusca x Vitis riparia*)) pomace, and apple (*Malus domestica* cv. Jonagold) and yellow pitahaya (*Hylocereus megalanthus*) peel, core, peduncle and seed mixture.	Cellulase and pectinase cocktails from *R. miehei* NRRL 5282 and *Aspergillus niger*, respectively.	Release of free phenolic compounds.	Increase the antioxidant effects of the phenolics as established by 1,1-diphenyl-2-picrylhydrazyl radical inhibition or ferric reducing antioxidant action analyses.	[37]
Watermelon (*Citrullus lanatus* Thunb) rind (WMR)	Enzyme cocktail composed of pectinase, endo-1,3 (4)-β-glucanase, α-amylase, endo-1, 4-β-xylanase and bacillolysine (protease).	Release of antioxidant phenolics up to 3 folds on fresh weight basis compared to conventional solvent extraction with substantial level of all phenolics.	WMR extracts retained most of their antioxidant properties.	[44]
Pigmented and non-pigmented rice bran	Cellulase and/or xylanase.	Rise in the quantity of soluble oryzanol.	Rise in the free radical scavenging activity and total antioxidant effect.	[45]
Guava (*Psidium guajava*) leaves	Xylanase, cellulase and β-glucosidase.	Enhanced the soluble phenolics content and flavonoids quantities by 103.2% and 81.6%, respectively.	Higher antioxidant effect and preventive action against supercoiled DNA harm.	[46]
Ulmus pumila barks (UPB)	Cellulase, pectinase and β-glucosidase.	Higher extraction yield of total phenolic compounds (TP).	Higher in vitro antioxidant activity was observed using the Fluorescence Recovery After Photobleaching (FRAP) and DPPH methods.	[47]

Table 2. *Cont.*

Food/Substrate	Enzyme	Chemical Effects	Bioactive Effects	Reference
Black tea leftover (BTLO)	Kemzyme, alcalase, acid cellulase, Pectinex and viscozyme	The hydrolysis of BTLO with 2.9% (*w/w*) kemzyme at 45 °C and pH 5.4 for 98 bettered the release of non-extractable polyphenols (NEPPs). The polyphenols extracts obtained by SC-CO_2 + EtOH were cleaner and richer in polyphenols compared to those obtained by CSE.		[48]
Cherry (*Cerasus pseudocerasus G. Don*) seeds	The enzyme cocktail included cellulase, hemicellulase, and pectinase.	More bioactive components (like a-tocopherol, b-carotene, phospholipids and phytosterols) were obtained.		[49]
Pomegranate (*Punica granatum*) peel extracts	Pectinase and cellulase.	Enzymatic extraction did not increase the extraction returns.	Selective antimicrobial activity against *S. aureus*, *Methycillin-resistant Staphylococcus aureus* and *Listeria monocytogenes.*	[50]
Seeds of *Cuscuta chinensis* Lam.	Cellulase and proteases.	The combination of enzymes supplied greater flavonoid yields than separate enzyme treatment.	The antioxidant effects of the flavonoids were directly related with their quantities as measured by the scavenging activity of (DPPH) free radical.	[51]
Sargassum muticum: whole algae (Sm) and residual algae from alginate production (AESm).	Alcalase, alcalase + Protamex, amylase, Protamex, celluclast, Rapidase Press, Rapidase TF, Rapidase UF L and Viscozyme L.	Higher yield.	One gram of extract was corresponding to 30 mg of ascorbic acid and 200 mg Trolox. The treatments did not influence the antagonist effect of *Sarsgassum muticum* aqueous isolates on melanoma and liposarcoma cells.	[52]
Crude and waste seeds of guarana (*Paullinia cupana*)	Aqueous enzymatic maceration (AEM) using cellulase and pectinase.	AEM enhanced the overall produce in the extract but did not efficiently extracted bioactive molecules from guarana seeds.		[53]
Longan (*Dimocargpus longan* Lour.) pulp	Superfine grinding-assisted enzymatic treatments (LP-SE) using cellulase.	Yield, sugar quantity, solubility, arabinose and mannose proportion increased but the apparent viscosity, particle size and glucose percentage decreased.	Strong stimulation on the abundance of *Lactobacillus plantarum*, *L. bulgaricus*, *L. fermentum* and *Leuconostoc mesenteroides*.	[54]
Soy pulp by-product (okara)	Endoproteases	Half of the initial insoluble proteins were turned into water-solvable peptides. The solubilization of isoflavones caught in the unsolvable protein matrix was detected too.	Higher antioxidant effectiveness than the initial substance.	[55]
Sesame (*Sesamum indicum* L.) bran	Viscozyme L., alcalase, ultrasound and ultrasound-supported enzymatic extractions.	Alcalase had higher protein and total phenolic compounds recovery than viscozyme L.	The highest antioxidant capacities (determined with the DPPH method and the 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) method) were found in the ultrasound-assisted enzymatic extraction.	[56]
Grape pomace and wheat bran	Two enzymatic cocktails obtained from the solid fermentation of grape pomace and wheat bran and only wheat bran by the altered strain *Aspergillus niger* 3T55B8 were used.	Total phenolic quantity augmented with the rise of time of enzyme production in all mediums. The activities of polygalacturonase and tannase showed a linear correlation with phenolic substances and proanthocyanidins, correspondingly.	Higher antioxidant potential.	[57]

Table 2. *Cont.*

Food/Substrate	Enzyme	Chemical Effects	Bioactive Effects	Reference
Leaves of *Viscum coloratum* (Kom) *Nakai* (VCP)	Cellulase.		The VCP extract hampered the replication of HBV-DNA and the emission of HBV antigens and showed a better antioxidant capacity.	[58]
Watermelon (*Citrullus lanatus*)	A papain digestion process was employed.		PWR showed antagonic ability to human laryngeal carcinoma Hep-2 cell in a dose and time depending way.	[59]
Alfalfa (*Medicago sativa* L.)	The enzyme complex used consisted of cellulose, papain and pectinase.	Different proportions of monosaccharides (glucuronic acid, glucose, rhamnose, galactose and xylose).	Ultrasonic enzyme-aided extraction had the greatest extraction yield, the greatest uronic acid quantity and the best antioxidant effects.	[60]
Japanese grape (*Hovenia dulcis*)	Cellulase generated by *Bacillus amyloliquefaciens* DL-3.	The enzymatic process augmented the release of sugars and diminished the removal temperature and time use for extraction.		[61]
Grape (*Vitis vinifera* I.) pomace of Syrah Cabernet Sauvignon, Malbec Pinot-Noir and Marselan varieties.	Pectinase and cellulase from *Aspergillus niger*; and tannase from *A. oryzae*.	The enzymatic treatment augmented by 66% the extraction of phenolics. Tannase released gallic acid and cellulase *p*-coumaric acid and malvidin-3-*O*-glucoside.	The enzymatic treatment increased the antioxidant capacity by up to 80%.	[62]

Direct treatments with enzymes (carbohydrate-cleaving enzymes mostly) are also used in preparations to release the phenolic aglycones [37]. Fungi species such as *Rhyzopus oryzae*, *Rhyzopus oligosporus* and *Aspergillus oryzaei* are used for solid state fermentation in several cereals [7]. These authors concluded that, although antioxidant effects of cereals can be enhanced through solid-state fermentation, these properties vary among fungi species and grains. It is also possible that some other metabolic pathways could be involved in solid-state fermentation besides the enzymatic release of phenolic compounds [5]. Shin et al. employed *Aspergillus awamori* and *Aspergillus oryzae* in order to ferment black rice bran (BRB) for 5 days. They found that although a moisturizing and autoclaving pre-treatment before fermentation lessened total phenolic content (TPC), fermentation boosted TPC specially protocatechuic acid and ferulic acid, which displayed the most considerable raises [63]. Wang et al. fermented guava leaves (GL) utilizing *Monascus anka* and *Bacillus* sp. and found that the fermenting process affect the composition and quantities of biochemical substances. Specifically, quercetin, kaempferol, gallic acid and quercetin-3-O-α-L-arabinopyranoside were the pointer elements accountable for the variations in the bioactivities of GL throughout fermentation; total flavonoids and phenolics content, kaempferol and quercetin correlated with their bioactivities very well [64].

During fermentation, the glycosylation degree of phenolic compounds changes and in consequence their bioactivity. For example, Wang et al. used complex enzyme-assisted extraction (CEAE) in guava leaves (GL) to heighten the biodisponibility of insoluble-attached phenolic compounds. By using this enzymatic treatment these authors found that the soluble phenolics content, the flavonoids content, as well as the ABTS, DPPH and FRAP improved greatly by 103.2%, 81.6%, 104.4%, 126.5% and 90.3%, correspondingly. Total water-solvable phenolics isolates from GL after CEAE displayed the maximum antioxidant actions and protective effects against supercoiled DNA harm. In the same way, quercetin and kaempferol contents augmented their bioactivity by 3.5 and 2.2 fold, respectively. They also found that after the CEAE, most of the phenolic substances were in their solvable form and scarcely in their insolvable-attached form [64].

3.3. Accumulation of Phenolic Acids in Fungi Cell Walls

In general, fungal endophytes coexists asymptomatically with their hosts and they represent an underused set of microorganisms for the detection of novel valuable substances because they can create different metabolites and have the capacity to synthesize substances that are only generated

and isolated from more complex plants [65]. In the same manner, the antioxidant effects of fungal endophytes from therapeutic plants has gained recognition in natural product investigation during the last decades. The antioxidant compounds synthetized by fungal endophytes probably support host plants to neutralize free radicals. Fungal endophytes have the ability to provide useful forbearance to free radicals under abiotic stress circumstances and they also can encourage development through biosynthesis of plant hormones and the attainment of nutrients [15].

Edible fungi contain bioactive glycolipids, aromatic phenols, fatty acid derivatives, polyacetylamine, poliketides, shikimic acid derivatives, sesquiterpenoids and many others [66]. Yeasts are enclosed by an inflexible cell wall, which is about 25–30% of the cell's dry weight. Polysaccharides extracted from yeasts' cell walls have showed important properties for human health beyond their function as structural organ, such as antioxidant, antiproliferative and immunomodulatory. For example, Galinari et al. studied the pharmacological properties of the α-mannan-rich fraction of the cell wall of the yeast *Kluyveromyces marxianus* CCT7735 in order to evaluate its chelating and cytotoxic activities [67].

Phenolic acids are commonly found in their free form in fungi and there is evidence that they are absorbed by the human body in their free form as well. After being ingested, they are absorbed and conjugated (glucuronated mainly) in the same pathways as flavonoids and other polyphenols [16]. In contrast to phenolic acids, flavonoids are not found in fungi fruiting bodies, since edible fungi lack the key enzymes implicated in the flavonoids metabolic route and they are not able to store the flavonoids present in growth substrates [68,69].

4. Bioavailability and Digestibility of Bound Phenolics

Bioavailability of phenolic compounds is essential for their biological properties. Plants, grains and vegetables in general have a tendency to have elevated quantities of phenolic acids but they are mainly in biologically unavailable and in an insoluble-bound structure. In maize, for example, the majority of the phenolic acids are insoluble-linked hydroxycinnamic acids. Through the effect of different processing technologies (such as nixtamalization, extrusion/cooking and steaming/autoclaving) many of these insoluble-bound phenolics are converted to their bioavailable, soluble state [70].

Phenolic acids are metabolized and move through the organism in their sulphated, methylated and glucuronated forms that affect their bioactivity. This process is very important because it involves not only detoxification, but also because it increases the hydrophilicity of phenolics to facilitate their elimination via urine and billis. For example, in plasma from patients who had consumed a specific amount of coffee, numerous methylated, sulphated and glucuronated metabolites of phenolic acids were found [16]. Additionally, polyphenols found in plasma are conjugated derivatives attached to albumin. In general, polyphenols are excreted through the biliary route toward the duodenum where they are subjected to the action of bacterial enzymes, specially b-glucuronidase. After the action of enzymes on them, polyphenols can be absorbed again, which can cause a lengthier occurrence of these compounds inside the organism [16].

Humans lack β-glucosidases and esterases to degrade dietary fiber that is water-insoluble and highly cross-linked. To improve bioavailability, it is convenient to transform insolvable cereal phenolics into solvable type; this process increases the health benefits obtained from cereal phenolics consequently [7]. Free phenolic acids are swiftly immersed by the small intestine and subsequently conjugated [16]. Conjugated phenolics have more potent antioxidant activity than free phenolic compounds [41].

5. Release of Soluble Conjugated Phenolics during Fermentation and Role of Microbiota

Gastro-intestinal microbiota is present all along from the mouth to the anus and it is composed by microorganisms (such as bacteria, fungi, viruses and archaea); bacteria being the majority group overwhelmingly. Microbiota is an ecosystem which is partially stable and bacteria here can resist important changes that happen in their dynamic environment [34]. These modifications in the

configuration of microbiota in humans can be understood in terms of diet, the influence of the immune system, chemical contacts or initial impacts of original colonizers [71].

Commonly, phenolics that are found in food are found as glycosides, esters or polymers that cannot pass through enterocytes, and thus, they have to be hydrolyzed by enzymes in the colon or they also can be catabolized by microbiota before their absorption [72]. For example, it has been revealed that existence of an extremely complicated xylan-decomposing system inside the large intestinal microbiota that can identify separate types of intricate carbohydrates and can react suitably [73]. Polymerized polyphenols such as ellagitannins and proanthocyanins (commonly present in walnuts and pistachios) can be digested by microbiota present in the colon, and subsequently, providing a large range of low molecular weight phenolic metabolites (such as alkylphenols, tyrosols and phenolic acids) that seem to alter the microbial ecosystem, including its profile, which causes prebiotic effects too [74]. All these processes carried out by gastro-intestinal microbiota also conducts to the biosynthesis of short-chain fatty acids and the liberation of attached phenolics (or non-extractable-polyphenols) [75].

The chemical structures of phenolic substances have impact over the conjugation reactions and also over the quantity of metabolites generated by the microflora in the colon. An example of this is chlorogenic acid, because the bound ester has the ability to modify its biological characteristics; the only local reaction in the human body where chlorogenic metabolism is involved takes place in the colon and is performed by bacteria because there are no esterases in the human organism that can free caffeic acid from chlorogenic acid. In the same way, ferulic and other hydroxycinnamic acids attached to cell walls cannot be released by human enzymes; to liberate these compounds, microbial enzymes from the colonic microflora are needed, such as esterases and xylanases. However, when these molecules are hydrolyzed by microbial enzymes, the efficiency absorption decreases because they can decompose aglycones and simple aromatic acids are released. Because of this, the absorption efficiency of phenolic acids is notably reduced when they are in their esterified form rather than in their free structures [16].

Bioavailability of anthocyanins is commonly low but through gut fermentation, the microbiota increase the bioavailability and in consequence the antioxidant and antidiabetic properties [76]. Intestinal metabolites of blackberry anthocyanins enhance the glucose consumption and glycogen content in HepG2 cells and show important antioxidant properties [77]. Microbiota plays a key role in intestinal fermentation of polyphenols, such as anthocyanins and isoflavones, which transform them into lower-molecular weight phenolics. Protocatechuic aldehyde and 4-hydroxybenzoic acid are byproducts of intestinal fermentation of anthocyanins while into equol- or *O*-desmethylangolensin come from isoflavones [78].

6. Conclusions

SSF processes using lignocellulolytic fungi not only have been proved to be more sustainable than traditional fermentations, but they also yield higher amounts of valuable compounds as well as higher bioactivities of these substances. Additionally, there is a lot of potential to identify other metabolites besides those that the fungi release from the substrate with enhanced bioactivity. Fungal polysaccharides also have prebiotic effects to treat or prevent chronic diseases.

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