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REVIEW ARTICLE

Recent developments and innovations in solid state fermentation

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Abstract After forty years of research development, an overview of solid-state fermentation (SSF), focusing on its applications, mainly of the very recent papers of the last five years, is presented. This review comprises the most important developed processes concerning the production of enzymes, biopulping processes, and traditional processes, for food fermentation, such as the production of Chinese *daqu* and *koji*, and industrial important biomolecules such as organic acids, pigments, phenolic compounds, aromas and biosorbents. SSF bioreactors design that has been developed is reported, so as the solutions for the classical drawbacks and the most important cases of successful employment of the technique are described. And, finally, it is summarized a very interesting report of patents and innovations regarding SSF products and processes.
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Introduction

Solid state fermentation (SSF) is a process in which microorganisms grow in an environment without free water, or with very low content of free water. Its historical importance for humankind date from thousands of years ago, mainly for food processing, both in western (bread and cheese) and eastern (Koji) countries. Considering the last century and the recent decades it is still used for production of important biomolecules and products for many industries, including food, pharmaceutical, textile, biochemical and bioenergy, among others (Pandey, 2003; Soccol & Vandenberghe, 2003).

The main counterpart for SSF is the submerged fermentation (Smf), a process in which microorganisms grow in liquid medium, with high content of free water. Biological processes carried out in Smf have notable advantages regarding instrumentation and control (monitoring of pH, dissolved oxygen, temperature, concentration of water soluble molecules), separation of biomass after the fermentation, mixing, aeration and scaling up (Farinas, 2015). Contrarily, SSF mimics the natural habitat of most part of microorganisms (mainly fungi and mold); demand less

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energy for sterilization (because of lower water activity); is less susceptible to bacterial contamination; regarding the products, it enables higher enzymatic productivity for many enzymes, it is less susceptible to substrate inhibition, and hence it allows higher final concentration of products; has several environmental advantages, since it allows the use of solid agro-industrial wastes as substrate and/or energy source in their natural form and facilitates the solid waste management, besides lesser wastewater production (Singhania, Patel, Soccol, & Pandey, 2009). Other aspects cited as positive concerning SSF are: the higher quality and higher activity of extracts; no need of organic solvents (which generally confer some level of toxicity for the extract); lower capital and operating costs; reduced downstream processing and reduced stirring (Martins et al., 2011; Singhania et al., 2009).

Considering historical aspects, the perspectives, and also taking into account the high density of papers about SSF, this article aims to present an overview of the subject including the main applications, of the last five years, and an interesting summary of patents and innovations developed in the area.

Microorganisms

The most important factors to be considered during the development of a SSF are the choice of microorganisms and the choice of substrates. Microorganisms that are particularly suitable for SSF are the filamentous fungi, since the technique simulates their natural habitat. In this condition, they are able to synthesize considerable amounts of enzymes and other metabolites (Farinas, 2015). Although filamentous fungi are considered the most appropriate microorganisms for SSF, and secondly the yeasts, which are also able to grow in a low water activity environment, there are also some species of bacteria (e.g. *Bacillus subtilis*, *Bacillus thuringiensis* and *Lactobacillus* sp.) which have been reported to successfully produce enzymes in solid-state condition (Singhania et al., 2009). Actinomycetes such as *Streptomyces* sp. are also indicated for SSF processes since they present characteristics such as abundant colonization of solid residues, production of a wide range of degradative enzymes and high resistance to extreme conditions (Orozco et al., 2008).

Substrates

The most promising residues for SSF include agricultural and forestry residues, which are very abundant and normally underutilized. A fraction is used to generate electricity, while another large fraction that is burned without energy recovery or remains in the field, representing an environmental problem (Farinas, 2015). Agro residues that can be used as substrates for SSF include sugarcane bagasse, cassava bagasse, cereal brans such as wheat bran, rice bran, oat bran and soybean bran, coffee pulp and husks, fruit peels and pulps, corn cobs, straws and husks of different origins. These materials are basically composed by cellulose, hemicellulose, lignin, starch, pectin and other fibers (Farinas, 2015; Singhania et al., 2009; Soccol & Vandenberghe, 2003).

The choice of the most appropriate microorganisms to be cultivated in the agro residue depends much on its composition. In the case of lignocellulosic residues, the wood rotting fungi are usually the most indicated. Wood rotting fungi can be classified in white-rot fungi (Basidiomycetes and some Ascomycetes), which preferentially degrade lignin, brown-rot fungi (Basidiomycetes), which degrade cellulose and hemicelluloses, and the soft-rot fungi (e.g. *Aspergillus niger* and *Trichoderma reesei*), which secrete a complete system of cellulases (Yoon, Ang, Ngoh, & Chua, 2014).

Usually, these agro residues are not only a solid support for nutrients absorption and biomass growth, but they are also a source of carbon and nutrients. Sometimes, supplementation is needed in order to provide all necessary nutrients for optimum growth. Macro and micronutrients that are usually added to the medium include phosphorus, sulfur, potassium, magnesium, calcium, zinc, manganese, copper, iron, cobalt, and iodine (Farinas, 2015; Pandey, 2003; Soccol & Vandenberghe, 2003).

Cost and availability are the main factors to be considered in the choice of a residue as substrate or support in SSF. However, other characteristics such as crystallinity, accessible area, surface area, porosity, and particle size are important aspects to be considered for SSF process (Farinas, 2015; Singhania et al., 2009).

Applications of SSF

Enzymes

The majority of SSF scientific papers, which were published in the last five years, are related to enzyme production, mainly cellulases and xylanases production. The class of the cellulases is formed by endoglucanases (EC 3.2.1.4) that cleave randomly the cellulose chain, exoglucanases (EC 3.2.1.74 and EC 3.2.1.91), which catalyze the hydrolysis of chain ends, and β-glucosidases (EC 3.2.1.21), also called cellobiases, that hydrolyse the product of the exoglucanases releasing glucose monomers (Kuhad et al., 2016). Xylanases are a class of enzymes that catalyze the hydrolysis of 1,4-α-D-xylosidic linkages in xylans, one of the components of the hemicellulose fraction of plant cell walls. Carboxy methyl cellulase (CMCase) activities between 172 U/g and 545 U/g were obtained, which represents the activity of endoglucanases, produced from substrates such as wheat bran, corn stover and apple pomace by filamentous fungi (*A. niger*, *Aspergillus fumigatus* and *Rhyzopus oryzae*). For xylanase, activities as high as 73,000 U/g or 98,000 U/g were reported, this time by *Bacillus* species cultivated on wheat bran (Table 1). Both classes of enzymes have important applications in the conversion of biomass to products such as ethanol, and also other important applications in the textile, paper, food and beverages industries.

Proteases were the third most studied group of enzymes produced by SSF in the recent literature. They were produced from various agro industrial and also from tannery industry wastes, especially by fungi of the genus *Aspergillus*. Activities higher than 3000 U/g and higher than 50,000 U/g were reported (Table 1). Proteases are considered the most significant industrial enzymes, representing around 60% of the global market, with applications in detergents,

Table 1 Reports of enzyme production in SSF in the last 5 years.

Product	Microorganism	Substrate/support	Productivity	Bioreactor	Reference
Enzymes					
Amylase	*Bacillus licheniformis* AT70	Date waste	209 U/g, 7 days	Flasks	Afrisham, Badoei-Dalfard, Namaki-Shoushtari, and Karami (2016)
Amylase	*Bacillus* sp. BBXS-2	Wheat straw	6900 U/g, 5 days	Flasks	Qureshi et al. (2016)
Amylase	*Macrophomina phaseolina*	Apple pomace	3309 U/g, 120 h	Flasks	Kaur, Dhillon, Brar, and Chauhan (2012)
Amylase	*Aspergillus oryzae*	Wheat bran	1491 U/g, 3 days	Flasks	Chen et al. (2014)
Amylase	*Thermomyces* sp.	Soy and bread waste	39,900 U/g, 4 days	4.5 L cylindrical reactor	Cerda, El-Bakry, Gea, and Sánchez (2016)
Amylase	*Aspergillus oryzae* S2	Starch and soybean meal	22,118 U/g, 12 days	Flasks	Sahnoun et al. (2015)
Cellulase	*Rhizopus oryzae* SN5	Wheat bran	437 U/g, 5 days	Flasks	Pandey, Edgard, and Negi (2016)
Cellulase	*Aspergillus fumigatus*	Corn stover	526 U/g (CMCase), 145 U/g (FPase), 4 days	Flasks	Liu et al. (2011)
Cellulase	*Aspergillus niger* NRRL 2001	Apple pomace, rice husk and lactoserum	401 U/g (FPase), 545 U/g (CMCase), 285 U/g (β-glucosidase), 96 h	Tray-type	Dhillon, Brar, Kaur, Metahni, and M'hamdi (2012)
Cellulase	*Aspergillus niger* NRRL-567	Apple pomace	134 U/g (Fpase), 60 U/g (β-glucosidase), 172 U/g (CMCase), 48 h	Flasks	Dhillon, Kaur, Brar, and Verma (2012)
Cellulase	*Aspergillus niger* NS-2	Wheat bran	395 U/g (CMCase), 28 U/g (FPase), 46 U/g (β-glucosidase), 96 h	Flasks	Bansal, Tewari, Soni, and Soni (2012)
Laccase	*Trametes versicolor* ATCC 20869	Brewer's spent grain	13,506 U/g, 12 days	Tray-type	Dhillon, Kaur, and Brar (2012)
Laccase	*Pleurotus ostreatus*	Sugarcane bagasse	167 U/g, 5 days	Flasks	Karp et al. (2012)
Laccase	*Pleurotus* sp.	Coconut coir	54,600 U/g, 8 days	Tray-type	Bhattacharya, Garlapati, and Banerjee (2011)
Laccase	*Pleurotus ostreatus*	Wheat bran	32,450 U/g, 7 days	Flasks	El-Batal, ElKenawy, Yassin, and Amin (2015)
Laccase	*Pyrenophora phaeocomes*	Rice straw	10,859 U/g, 4 days	Flasks	Rastogi, Soni, Kaur, and Soni (2016)
Laccase	*Coriolus* sp.	Wheat bran	2661 U/g, 10 days	Flasks	Mathur, Mathur, Sharma, and Chauhan (2013)
Laccase	*Ganoderma lucidum* and *Saccharomyces cerevisiae*	Glucose	38,000 U/L, 8 days	Biomembrane-surface liquid co-culture (BSLCc), 100 L	Hailei, Chaozhi, Guangli, and Ping (2013)
Lipase	*Penicillium simplicissimum*	Castor bean waste	155 U/g, 96 h	Tray-type	Godoy, Gutarra, Castro, Machado, and Freire (2011)
Lipase	*Pseudomonas aeruginosa* PseA	Deoiled *Jatropha curcas* seed cake	932 U/g, max. 9 days	Flasks	Joshi, Mathur, and Khare (2011)

Table 1 (*Continued*)

Product	Microorganism	Substrate/support	Productivity	Bioreactor	Reference
Lipase	*Burkholderia cenocepacia*	Sugarcane bagasse, sunflower seed and olive oil	72.3 U/g, 96 h	Flask	Liu, Li, Meng, and Yan (2016)
Lipase	*Schizophyllum commune* ISTL04	*Leucaena leucocephala* seeds	146.5 U/g, 5 days	Flasks	Singh, Singh, Kumar, and Thakur (2014)
Lipase	*Thermomucor indicae seudaticae* N31	Sugarcane bagasse and soybean oil	15 U/g, 72 h	Polypropylene bags	Ferrarezi et al. (2014)
Pectinase	*Aspergillus oryzae* CPQBA 394-12 DRM 01	Citrus pulp and sugarcane bagasse	40 U/g, 18–24 h	Pilot scale packed-bed	Biz et al. (2016)
Pectinase	*Aspergillus niger* F3	Citrus peel	265 U/g, 96 h	Horizontal drum	Rodríguez-Fernández, Rodríguez-León, Carvalho, Sturm, and Soccol (2011)
Protease	*Aspergillus terreus* NCFT 4269.10	Chickling vetchpeels/grass pea peels (CVP)	5266.8 U/mL, 96 h	Static flasks	Sethi et al. (2016)
Protease	Consortium	Hair wastes from the tannery industry as substrate and anaerobically digested sludge as co-substrate	52230 U/g, 14 days (336 h)	10-L air tight reactors (batch fermentation)	Yazid, Barrena, and Sánchez (2016)
Protease	*Aspergillus niger* LBA 02	Wheat bran, soybean meal, cotton seed meal and orange peel	262.78 U/g, 48 h	Static flasks	Castro et al. (2015)
Protease	*Aspergillus oryzae* CCBP 001	Canola cake	From 355.5 U/g before spray drying. Activity of 1388.25 (after spray drying)	Laboratory scale system consisting of 16 columns (2.5 cm diameter, 20 cm length) placed in a water bath	Freitas et al. (2015)
Protease	*Aspergillus versicolor* CJS-98	*Jatropha* seed cake	3366 U/g, 96 h	Static flasks	Veerabhadrappa, Shivakumar, and Devappa (2014)
Protease	*Aspergillus oryzae*	Screw-pressed *Jatropha curcas* seed	3094 U/g, 96 h	Static flasks	Thanapimmetha, Luadsongkram, Titapiwatanakun, and Srinophakun (2012)
Protease and glucoamylase	*Aspergillus awamori*	Waste bread	102.8 U/g (glucoamylase), 63.7 U/g (protease), 168 h	9 cm Petri dishes	Melikoglu, Lin, and Webb (2013)
Protease	*Pleurotus sajor-caju*	Wheat bran, rice bran, green gram, corn flour and ragi	Around 85 U/mL, 192 h	Static flasks	Ravikumar, Gomathi, Kalaiselvi, and Uma (2012)
Xylanase	*Trichoderma viride*-IR05	Wheat bran, rice polish, rice husk, soybean meal, sunflower meal, sugarcane bagasse and corn cobs	72.4 U/g, 168 h	Static flasks	Irfan, Nadeem, and Syed (2014)

Table 1 (*Continued*)

Product	Microorganism	Substrate/support	Productivity	Bioreactor	Reference
Xylanase	*Aspergillus tubingensis* FDHN1	Sorghum straw	5177.23 U/g, 120 h	Static flasks	Adhyaru, Bhatt, Modi, and Divecha (2016)
Xylanase	*Bacillus* sp. PKD-9	Wheat bran	98000 U/g, 120 h	Static flasks	Panwar, Srivastava, and Kapoor (2014)
Xylanase	*Bacillus aerophilus* KGJ2	Wheat bran, tea dust, sawdust, paper waste, cassava bagasse, rice straw and rice husk	45.9 U/g, 24 h	Static flasks	Gowdhaman et al. (2014)
Xylanase, CMCase, FPase and B-glucosidase	*Aspergillus fumigatus* SK1	Untreated oil palm trunk	54.27 U/g (CMCase), 3.36 U/g (FPase), 4.54 U/g (β-glucosidase), 418.70 U/g (xylanase), 96 h	Static flasks	Ang, Shaza, Adibah, Suraini, and Madihah (2013)
Xylanase	*Aspergillus oryzae* (P6B2)	Wheat bran	2830.7 IU/g, 24 h	Lab-scale system consisting of 16 columns (2.5 cm diameter, 20 cm length) placed in a water bath	Pirota et al. (2013)
Xylanase and cellulase	*Aspergillus niger* FGSCA733	*Jatropha curcas* seed cake	6087 U/g and 3974 U/g of xylanase (48 h) and cellulose (120 h) respectively	Static flasks	Ncube, Howard, Abotsi, Jansen van Rensburg, and Ncube (2012)
Xylanase	*Promicromonospora* sp. MARS	Rice straw	85.0 IU/g, 96 h	Aluminum trays (5 cm × 2.5 cm × 2 cm)	Kumar, Joshi, Kashyap, and Khanna (2011)
Xylanase	*Bacillus pumilus*	Paddy husk (support); corncob as C source; groundnut powder or sesame seedcake powder or coconut seedcake powder or soy meal powder as N source	326.5 U/g, 144 h	Not informed	Kapilan and Arasaratnam (2011)
Xylanase and cellulase	*Rhizopus oryzae* SN5	Wheat bran	437.54 U/g (cellulase) and 273.83 U/g (xylanase), 120 h	Static flasks	Pandey et al. (2016)
Xylanase	*Aspergillus lentulus*	Wheat bran, corn cob, sugarcane bagasse and wheat straw	158.4 U/g, 96 h	Static flasks	Kaushik, Mishra, and Malik (2014)
Xylanase	*Bacillus pumilus* SV-85S	Wheat bran	73,000 U/g, 48 h	Static flasks	Nagar et al. (2011)
Xylanase	*Aspergillus candidus*	Wheat bran	770 U/g, 72 h	Static flasks	Garai and Kumar (2013)
Xylanase	*Thermoascus aurantiacus* var. *levisporus* KKU-PN-I2-1	Sugarcane bagasse and rice bran (1:1, w/w)	176 U/g, 196 h. After ion exchange chromatography 2560 U/g of protein	Static flasks	Chanwicha, Katekaew, Aimi, and Boonlue (2015)

$Y_{P/S}$, product yield from substrate ($g\,g^{-1}$).

leather processing, food and feed processing, pharmaceuticals, chemicals and waste treatment (Sethi, Jana, Nanda, Mohapatrac, & Sahoo, 2016).

Laccases (benzenediol:oxygen oxidoreductase, EC 1.10.3.2), which are polyphenol oxidases that find many applications in biopulping, biobleaching, detoxification of environmental pollutants, pharmaceuticals, preparation of beverages, among others (Dhillon, Kaur, & Brar, 2012), were produced from agro wastes such as sugarcane bagasse, wheat bran, rice straw, and brewer's spent grain. The highest reported activity was obtained with coconut coir fermented by *Pleurotus* sp. (54,600 U/g in 8 days, according to Table 1).

Lipases (triacylglycerol lipase, E.C. 3.1.1.3) were also produced from oily residues or fibrous residues enriched with oil, using both fungi (*Penicillium simplicissimum*, *Schizophyllum commune*, *Thermomucor indicae seudaticae*) and bacteria (*Pseudomonas aeruginosa*, *Burkholderia cenocepacia*), and activities between 15 U/g and 932 U/g were reported (Table 1). Applications of lipases include detergents, synthesis of pharmaceuticals, cosmetics, food processing, textile processing and, more recently, the synthesis of biodiesel (Ferrarezi et al., 2014).

Finally, amylases (E.C. 3.2.1.) were produced from residues such as wheat bran and straw, apple pomace, soy, bread and date waste, some of them enriched with starch, and different microorganisms were employed (*Aspergillus oryzae*, *Bacillus* spp., *Thermomyces* sp. and *Macrophomina phaseolina*). Highest activity (39,900 U/g in 4 days, Table 1) was obtained with soy and bread waste fermented by *Thermomyces* sp. Amylases are widely employed in the food industry, for ethanol production from starchy materials, and in pharmaceuticals, paper and detergents, representing around 30% of the global market of enzymes (Singh & Gupta, 2014).

Biopulping

Biopulping is a kind of biomass pretreatment that promotes the delignification of cellulosic material through the action of ligninolitic exoenzymes produced ''*in situ*'', which is normally performed by fungi that grow onto the solid ligninolitic material or a solid process fermentation. These enzymes act on the solid substrate, breaking the chemical bonds of the lignin molecule, depolymerizing the whole structure into smaller structures (Mendonça, Guerra, & Ferraz, 2002).

The fungus must be selected according its enzymatic activities, presenting a high laccase and peroxidase activity and a low cellulasic activity to preserve the cellulosic fraction. This leads to preferably digestion of the lignin that is present in the vegetable cell wall. Due to the mild conditions used, biopulping produces cellulose pulp demanding less energy and chemical products in a less severe process compared to the chemical or mechanical conventional pulping. Also, biopulping improves the cellulose recovering yield and the quality of the paper fiber (Fonseca et al., 2014). The most common and efficient fungi used are those of the wood decomposition, known as the white rot fungi and the brown rot fungi, that during their secondary metabolism secret these enzymes (Fernández-Fernández, Sanromán, & Moldes, 2013). *Trametes* e *Pleurotus* genus are the most studied such as *Trametes pubescens* (Galhaup, Goller, Peterbauer, Strauss, & Haltrich, 2002), *Trametes versicolor* (Font, Caminal, Gabarrell, Romero, & Vicent, 2003), *Trametes hirsuta* (Rodríguez-Couto & Toca-Herrera, 2006), *Pleurotus ostreatus* (Lenz–Hölker, 2004), but it can also be cited *Coriolus hirsutus* (Koroleva et al., 2002), *Pycnoporus cinnabarinus* (Meza, Auria, Lomascolo, Sigoillot, & Casalot, 2007), *Neurospora crassa* (Cabana, Jones, & Agathos, 2007; Luke & Burton, 2001).

The disadvantage of the biopulping is the time demanding for the process including time necessary to the fungus growth and the substrate colonization, so an alternative to turn the process faster is the application of the enzymatic ligninolitic ''pool'', produced in an optimized fermentative process. This enzymatic pretreatment was proposed as an alternative to the biological pretreatments that use the fungus application onto the material to be treated, slower due to the time demanding to the fungus growth and the difficulties to keep the process aseptic for long time periods (Martín-Sampedro, Eugenio, & Villar, 2012).

The enzymatic pulping besides replacing the fungus direct application and reducing the time necessary to the process, can also replace the chemical catalysts of the traditional thermochemical pulping, promoting the material's digestion in milder conditions. The production of the ligninolitic enzymatic pool is carried out in bioreactors under controlled and optimized conditions. The enzymatic broth produced can be composed by the desired enzymes according to the material to be treated and the fraction of the material is supposed to be preserved (Hyeon et al., 2014).

Starters in oriental and western countries

Many products employ ''starter cultures'' which are cultivated in SSF. These starter cultures are usually considered as one of the ingredients to prepare a broad set of products, such as liquors, vinegars, rice wines (e.g. the very well known *sake*), soy sauce (e.g. *shoyu*), distilled beverages (e.g. *shochu*), meat sauce and soybean paste (e.g. *miso*), among others. In western countries, it is usual to name all these starter cultures as *koji*, but in truth there are specific classifications, such as the Chinese *qus* (*daqu*, *Xiaoqu*, *Hongqu*, *Fuqu* and others), or the Korean *nuruk*. In most cases, the role of these starters is to produce enzymatic pools (mainly amylases, proteases, lipases) to hydrolyze substrate macromolecules (like starch, proteins, fatty acids) (e.g. rice, in the case of *sake*).

The traditional Japanese *koji* is prepared using soybean grains as substrate, or other cereals like wheat and rice. The process is generally uncontrolled, the environment must be warm and humid, and the most frequent mold find in *koji* is *A. oryzae*, although other *Aspergillus* sp. (notably *Aspergillus sojae*), *Rhizopus* sp., *Mucor* sp., *Monascus* sp. and *Penicillium* sp. are also found in several cases (Zhu & Tramper, 2013). The Korean *nuruk* can be prepared with a diversity of cereals, but traditionally it is wheat based. The micro flora is also diverse, but the common involved genera are: *Aspergillus*, *Mucarales* and *Rhizomucor*. It is used to prepare an alcoholic beverage, similar to *sake*, called *makgeolli* (Bal, Yun, Yeo, Kim, & Kim, 2016). The Chinese *daqu* is divided basically in four types (light flavor, strong

flavor, sauce flavor and miscellaneous flavor). Most of *daqu*s are prepared with barley and pea, and are used as ingredients for several types of vinegar and liquors, among other products. Depending on the stage of the *daqu* preparation, several groups of microorganisms can be found, including mesophilic bacteria and fungi, yeasts and molds, lactic acid bacteria, and even thermophilic *Bacillus* and fungi (mainly *Lichtheimia corymbifera*) (Zheng et al., 2014).

Recently, much attention has been paid to these starters. The following themes can be cited: cooking and mechanical conditions of fermentation (Jao, Ko, & Hsu, 2011); changes in environmental content affecting the flavor of products (Chen, Wu, & Xu, 2014); aroma development (Iizuka-Furukawa, Isogai, Kusaka, Fujii, & Wakai, 2016); detection and quantification and/or analysis of volatiles in koji derived products (Inoue et al., 2016; Moy, Lu, & Chou, 2012); different combinations of substrates for microorganism growth and/or biomolecules production (Chancharoonpong, Hsieh, & Sheu, 2012); production and/or role of enzymes (Kawauchi & Iwashita, 2014; Watanabe et al., 2011); metabolism of ferulic compounds – which confer off flavors in final products (Hashizume, Ito, Ishizuka, & Takeda, 2013; Ito, Suzuki, Nakayama, Ito, & Hashizume, 2014; Suzuki, Ito, Hiroshima, Tokiwano, & Hashizume, 2016); anti-cholesterol effect of koji derived products (Lim et al., 2015); antioxidant effect of koji derived products (Feng et al., 2014; Giri, Osako, Okamoto, Okazaki, & Ohshima, 2011; Huang, Lai, & Chou, 2011; Ohata, Uchida, Zhou, & Arihara, 2016; Okutsu et al., 2012, 2015); supplementation of koji derived products (Marui et al., 2013); analysis of secreted proteins and/or peptides in koji related products (Maeda, Okuda, Hashizume, Joyo, & Mikami, 2011; Zhang, Guan, Cao, Xie, & Lu, 2015); importance of symbiosis (Furukawa, Watanabe, Toyama, & Morinaga, 2013) and finally, special attention has been given for the identification of microbial community in these complex environments (Bal et al., 2016; Felder, Burns, & Chang, 2012; Kim et al., 2015; Lv et al., 2013, 2015; Takashita et al., 2013; Tanaka, Watanabe, & Mogi, 2012; Wei et al., 2013; Yamada et al., 2011; Yan, Qian, Ji, Chen, & Han, 2013).

Among the western classical products, the manufacturing of cheese can be cited as an example of classical employment of SSF. For some kinds of cheese, like the blue cheeses (e.g. *Roquefort*) and the soft cheeses (e.g. *camembert*) the ripening process is an important step, and can be either a spontaneous process, with naturally occurring strains or with selected starter cultures (SSC). In the last decades, food industry has focused attention on SSC for cheeses, in order to preserve safety and quality of the final product, besides its standardization (Bassi, Puglisi, & Cocconcelli, 2015). Regarding cheese and cheese-making process, papers in the last few years have reported the identification of the present microbiota (Gkatzionis, Yunita, Linforth, Dickinson, & Dodd, 2014), the gene transfer among fungi (Ropars et al., 2015) the activity of released enzymes (Ozturkoglu-Budak, Wiebenga, Bron, & de Vries, 2016), organoleptic and sensory characteristics (Galli, Martin, da Silva, Porto, & Spoto, 2016), the effect of milk treatment in the ripening process (Voigt, Patterson, Linton, & Kelly, 2011), dynamic mathematical modeling (Sicard, Baudrit, Leclerc-Perlat, Wuillemin, & Perrot, 2011), development of new tools for quality control (Sicard et al., 2012) and functional (neuroprotective) effects of produced metabolites (Ano, Hoshi, Kutsukake, & Nakayama, 2016).

Others

Many other applications can be found for SSF. Some of the most important ones are listed in Table 2, namely: organic acids production (Ali, Anwar, Irshad, Mukhtar, & Warraich, 2016; Das, Brar, & Verma, 2015; Das, Brar, & Verma, 2016; Dhillon, Kaur, Sarma, & Brar, 2013; Mai, Lee, & Choi, 2016; Raza et al., 2011); pigments production (Certík, Adamechová, & Guothová, 2013; Dursun & Dalgıç, 2016; Eryılmaz, Dursun, & Dalgıç, 2016; Haque, Kachrimanidou, Koutinas, & Lin, 2016; Srianta, Zubaidah, Estiasih, Yamada, & Harijono, 2016; Velmurugan et al., 2011); aroma production (Madrera, Bedrinana, & Valles, 2015); production/recovery of materials with potential use as biosorbents (Dhillon et al., 2016); production of phenolic compounds (Salar, Purewal, & Bhatti, 2016). Moreover, traditional processes, which are still being studied and improved by researchers: biobleaching (Cheng et al., 2012), ensiling (Ambye-Jensen et al., 2013; Franco, Buffiere, & Bayard, 2016; Kholif, Elghandour, Rodríguez, Olafadehan, & Salem, 2016) and composting (Fdez-Güelfo, Álvarez-Gallego, Sales, & García, 2012; Grujic, Dojnov, Potocnik, Duduk, & Vujci, 2015; Zhang, Zhang, Wang, Chen, & Wang, 2016). All these researches that are related to SSF bring light and new perspectives for important areas, such as food industry, tannery industry, animal feed industry, renewable energy industry and solid waste disposal/management.

Bioreactor design for SSF

Since Raimbault started to work with packed bed columns, the so called Raimbault columns, some SSF bioreactors models appeared, which are classified as follows. Actually, SSF bioreactors can be classified based on the mixing system that is employed: static bioreactors (fixed bed, perforated trays) or stirred bioreactor (horizontal drum or stirred drum). Other classifications can be also found according to the type of aeration (with or without forced aeration) (Durand, 2003; Bhattacharyya, Banerjee, & Ghosh, 2008; Spier, Vandenberghe, Medeiros, & Soccol, 2011) or employed mixing system (Singhania et al., 2009). These are the tray, packed-bed, horizontal drum and fluidized bed bioreactors having their own advantages and disadvantages, which promoted the necessity to develop novel bioreactors with better design. Durand (2003) has given relevant information on various designs of bioreactor for SSF. The design of bioreactors must take into account some peculiarities of the materials that are used as growth media, and their characteristics such as composition, size, strength, porosity and water holding capacity. SSF occurs in the absence of free water and filamentous fungi are the microorganisms that are naturally adapted to this fermentation technique. In this case, some details must be considered in bioreactor design such as fungus morphology, with respect to the presence of septate hyphae or not, which influences the choice of agitation (without stirring, stirring occasionally or continuously). Another point to consider is the aeration by diffusion or forced aeration. All these details certainly raise bioreactors complexity.

Table 2 Production of pigments, organic acids and other compounds by SSF in the last 5 years.

Product	Microorganism	Substrate/support	Productivity	Bioreactor	Reference
Pigments					
Pigments	*Monascus purpureus*	Rice, corn, whole sorghum grain, dehulled sorghum grain and sorghum bran	Highest peak is EMS ($\times 10^3$) 18895 for rubropunctamine, with rice as substrate	A jar with 20 g of substrate	Srianta et al. (2016)
Pigment (astaxanthin)	*Yamadazyma guilliermondii*, *Yarrowia lipolytica*, *Xanthophylomyces dendrorhous*, *Sporidiobolus salmonicolor*	Wheat wastes	109.23 μg/g, 12 days (288 h)	Static flasks	Dursun and Dalgıç (2016)
Pigment (astaxanthin)	*Xantophylomyces dendrorhous*, *Sporidiobolus salmonicolor*	Olive pomace	220.24 μg/g, 12 days (288 h)	Static flasks	Eryılmaz et al. (2016)
Pigments (red)	*Monascus purpureus* KACC 42430	Corn cob powder	25.42 OD units/g, 168 h	Static flasks	Velmurugan et al. (2011)
β-Carothene and γ-linolenic acid	*Mucor petrinsularis*, *Mucor dimorphosporus*, *Mucor circinelloides*, *Mucor hiemalis*	Wheat bran, rye bran, oat flakes, barley groats and spent malt grain	8.5 μg/g of β-carothene and 12.1 mg of γ-linolenic acid, 180 h	Autoclavable microporous polypropylene bags (160 mm × 270 mm)	Certík et al. (2013)
Pigment, glucoamylase and protease	*Monascus purpureus*	Bakery waste	24 AU (absorbance units)/g; 8 U and 117 U respectively for pigments, glucoamylase and protease, 168 h	Static flasks	Haque et al. (2016)
Organic acids					
Citric acid	*Aspergillus niger* NRRL 567	Apple pomace	294.2 g/kg of dried apple pomace, 120 h	12 L rotating drum type bioreactor	Dhillon et al. (2013)
Citric acid	Consortium of *Aspergillus ornatus* and *Alternaria alternata*	Apple pomace and peanut shell	13.32 mg/g of substrate, 48 h	Static flasks	Ali et al. (2016)
Fumaric acid	*Rhizopus oryzae* 1526	Pulp and paper solid waste	41.45 g/kg of dry weight substrate, 21 days (504 h)	Static flasks	Das et al. (2016)

Table 2 (*Continued*)

Product	Microorganism	Substrate/support	Productivity	Bioreactor	Reference
Fumaric acid	*Rhizopus oryzae* 1526	Apple pomace	52.0 g/kg of dry weight substrate, 21 days (504 h)	Plastic trays (35 cm × 22 cm × 11 cm)	Das et al. (2015)
Lactic acid	*Lactobacillus amylovorus*	Corn grits	$Y_{P/S}$ of 0.91 g/g	Lab scale stirred tank reactor	Trontel et al. (2011)
Poli-gamma-glutamic acid	*Bacillus amyloliquefaciens*	Dairy manure compost, soybean cake, corn flour, residues from production of monosodium glutamate, wheat bran and rapeseed cake	43.7 mg/g of substrates, 48 h	Static flasks	Yong et al. (2011)
Oxalic acid	*Aspergillus niger* van Tieghem KACC 44333	Corn cob powder	120 g/kg of dry weight substrate, 168 h	Static flasks	Mai et al. (2016)
Others					
Phenolic compounds	*Aspergillus awamori*	Pearl millet	176.82 mg GAE/g of dry substrate	Static flasks	Salar et al. (2016)
Volatile compounds	*Saccharomyces cerevisiae*, *Hanseniaspora valbyensis* and *Hanseniaspora uvarum*	Apple pomace	Esters, lactones, acids, terpenoids, aldehydes, ketones and alcohols – a total of 144 compounds were produced	30 L capacity high density polyethylene (HDPE) tanks equipped with an air-lock	Madrera et al. (2015)
Biosorbents	*Aspergillus niger*	Apple pomace	The different waste BMs, such as fungal biomass (living and dead), alkali insoluble material and acid and alkali insoluble material had their bioadsorbent potential (for metals) tested	12-L rotating drum type bioreactor	Dhillon et al. (2016)

$Y_{P/S}$, product yield from substrate ($g\,g^{-1}$).

Static bioreactors

Different types of static bioreactors are used for SSF from laboratory to industrial scale. Erlenmeyer flasks, small perforated trays, fixed bed bioreactors or Raimbault columns, Petri dishes, jars, Roux bottles and roller bottles offer the advantage of simplicity and the possibility to work with small volumes. The main characteristic of these bioreactors is the absence of agitation (Durand, 2003). Erlenmeyer flasks are very simple and are used in laboratory scale for initial studies and processes' conditions optimization. They are made of glass and have limited size. These flasks are closed with cotton plugs, which allow the aeration by diffusion. Some advantages are: easy of handle, low cost and allow multiple simultaneous tests. Different types of static bioreactors for SSF are presented below (Singhania et al., 2009; Spier et al., 2011).

Fixed bed bioreactors – the Raimbault columns

The Raimbault columns, packed bed or fixed bed bioreactors (Raimbault & Germon, 1976) are filled with the solid substrate or supports. The column bioreactors are closed systems with forced aeration. Columns are connected to air bubblers, and introduced into a water bath with controlled temperature. Aeration, made by saturated air that is pumped through the columns, is adjusted to the desired air flow and controlled with the help of a flowmeter attached to the column air outlet. This model of bioreactors allows the study of the influence of forced aeration on growth through the evaluation of respirometry (O_2 consumed and CO_2 produced) of the microorganism for the understanding of their metabolism. These bioreactors are the most employed in laboratory scale. A model of columns reactors made of glass coupled with a system that analyses the oxygen and carbon dioxide composition in the exhaust airflow from the column is shown in Fig. 1A. Limited bacterial contamination is observed due to the close system. Moreover, the same bioreactor can be used for both fermentation and extraction procedures of the final product (Singhania et al., 2009; Spier et al., 2011). The use of column reactors minimizes problems with temperature gradients, due to the convection caused by air entering the reactor. These bioreactors have been considered interesting due to process control, especially by removing heat (which does not happen efficiently in large-scale processes). Furthermore, the CO_2 released during metabolic reactions can be eliminated, allowing its replacement by air, which is an advantage for some processes. Temperature control is done by placing the reactor in a bath or using jackets with circulating coolant fluid. However, the reduction in porosity of the bed, with the progress of fermentation, is a problem to overcome in this type of bioreactor.

So the basic design feature of packed-bed bioreactors is the introduction of air through a sieve which supports the substrate. In this way, a bioreactor was developed at pre-pilot scale (Fig. 1C) for defining the control strategy and optimizing the air-inlet temperature, the airflow rate, the addition of water and agitation during a SSF process. Located in a clean room, the reactor can be pasteurized in situ by steam generated by the water-bath used for the air humidification. This reactor is very simple and can process a few kilograms of dry solid medium. An adaptation of packed bed bioreactors would be the insertion of mixing coupled with forced aeration, which could increase the homogeneity of the cell population. The geometry of the stirred bed reactor is similar to that used in fixed bed, but includes a mixing system. In this case, the great advantage of this system would be the possibility to work with higher scales (Singhania et al., 2009; Spier et al., 2011).

Perforated trays bioreactors

Tray bioreactors are simple systems in which the substrate is laid out on trays, made by wood or stainless steel, which are perforated to facilitate air convection Fig. 1B. The substrate is placed in the tray in thin layers (from 5 to 15 cm) that are arranged with a space between them to allow the aeration. Trays are arranged in a chamber or room with controlled temperature and humidity. This model is easy to scale-up, but requires large areas for operations, intensive labor and difficulties with contamination control (non sterile processes). Problems can also occur with oxygen transfer, which depends on tray characteristics and the height of the substrate layer. When the substrate is inoculated, the oxygen concentration is uniform. Then, the formation of the mycelium changes the porosity and thus the effective diffusivity. The release of CO_2 and heat also limit the transport of O_2 and the creation of higher O_2 gradients that are inevitable, especially for higher substrate layers.

Agitated bioreactors

Another concept of bioreactors for SSF, which was based on continuous or intermittent agitation of the solid medium, was also developed (Durand, 2003; Spier et al., 2011; Thomas, Larroche, & Pandey, 2013). The bioreactors can be a rotating drum or horizontal paddle mixer with or without a water-jacket. When working with continuously mixing, it is expected to increase the homogeneity of the solid medium and better oxygen transfer to the microorganism.

Koji bioreactors

An example of static non-sterile bioreactor is represented by the rotary type automatic *Koji* making equipment marketed by Fujiwara in Japan (Fig. 2A). The treated substrate is heaped up on a rotary disk. Depending on the diameter of this disk, different working volumes are available but always with a layer of maximum thickness 50 cm. This non-sterile reactor operates with a microcomputer which controls all the parameters (temperature of the air-inlet, air flow rate and agitation periods). The main drawback of this equipment is the need to prepare and inoculate the substrate in other equipment before filling the reactor. Nevertheless, this type of design is widely used in Asian countries (Durand, 2003; Singhania et al., 2009; Spier et al., 2011).

Horizontal drum

Horizontal drum bioreactors are built in drum-shape and contain baffles for agitation of the medium (Fig. 2B). The agitation in this type of reactor can be continuous or sporadic, and may lead to problems of shear and damage of the mycelium structure. The schematic system is showed in

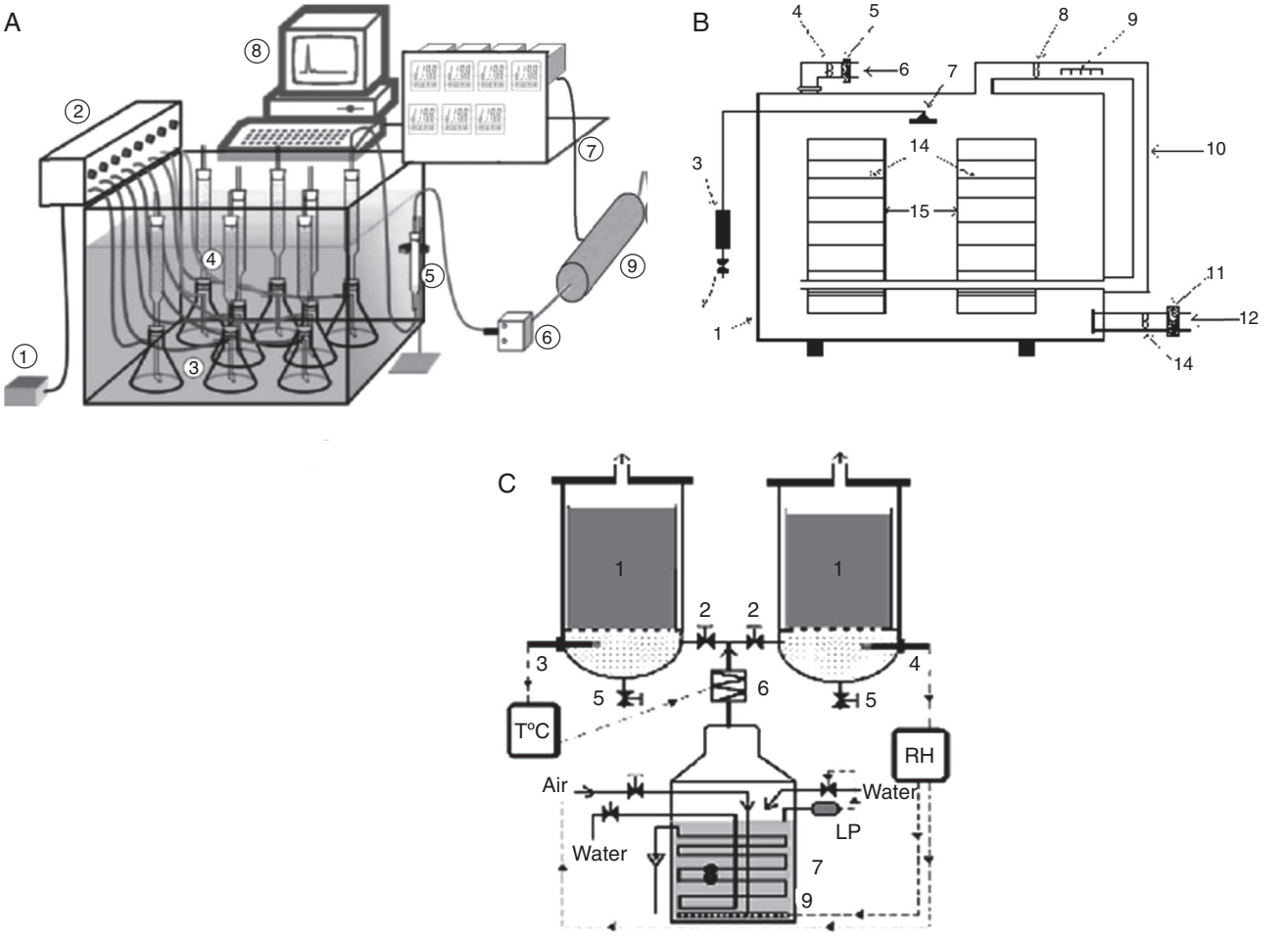


Figure 1 (A) Lab-scale fixed bed bioreactors apparatus for solid state fermentation: (1) air pump; (2) air distribution system; (3) humidifiers; (4) fermentation columns immersed in a water bath with controlled temperature; reactor; (5) filter; (6) flow sensor; (7) controllers display; (8) computer with data acquisition and control software; (9) cylindrical sensor base, where the following sensors are installed: CO_2 and O_2, humidity and outlet temperature. (B) Perforated trays bioreactor. (C) Unmixed bioreactors with forced aeration. (1) Basket containing the solid medium, (2) valves for airflow adjustment, (3) air temperature probe, (4) relative humidity probe, (5) draincocks, (6) heating box, (7) humidifier, (8) coil for circulation of cold water, (9) resistive heater. Sources: modified from Durand (2003), Spier et al. (2011) and Singhania et al. (2009).

Fig. 2B. This bioreactor has been used for solid-state fermentation since the 1930s (Durand, 2003).

Mixing bioreactor

A 50 L bed bioreactor was patented by Durand (2003). This reactor, which has a planetary mixing device (Fig. 2C) and is completely automatic for the different process steps: sterilization of the bioreactor, sterilization of the medium, process control during fermentation and data acquisition.

Rotating drum

Rotating drum bioreactors (RDB) consist of an horizontal cylinder, where the mixing is provided by the tumbling motion of the solid medium, which may be aided by baffles on the inner wall of the rotating drum (perforated or not). However, in all these reactors, the mixing is less efficient than with a paddle mixer. RDBs provide relatively gentle and uniform mixing by improving baffle design, since there is no agitator within the substrate bed (Fig. 2D). The engineering principles of RDB have received interest for biofuels production using cellulosic materials (Durand, 2003; Spier et al., 2011). Rotating drum bioreactors with air circulation and continuously mixing are commonly used in pilot or lab scale process. According to Durand (2003) the largest reactor cited in the literature was a 200 L stainless steel rotating drum, which used 10 kg of steamed wheat bran as substrate for kinetic studies of *Rhizopus*.

Scale-up aspects

Although scale-up methods for SmF are well developed, these methods cannot be applied directly to SSF bioreactors: due to the differences in the physical structures of the systems (Pandey, 2003; Singhania et al., 2009; Soccol & Vandenberghe, 2003). The major problems to overcome are related to the engineering aspects, such as lack of standardized processes and limited reproducibility of the

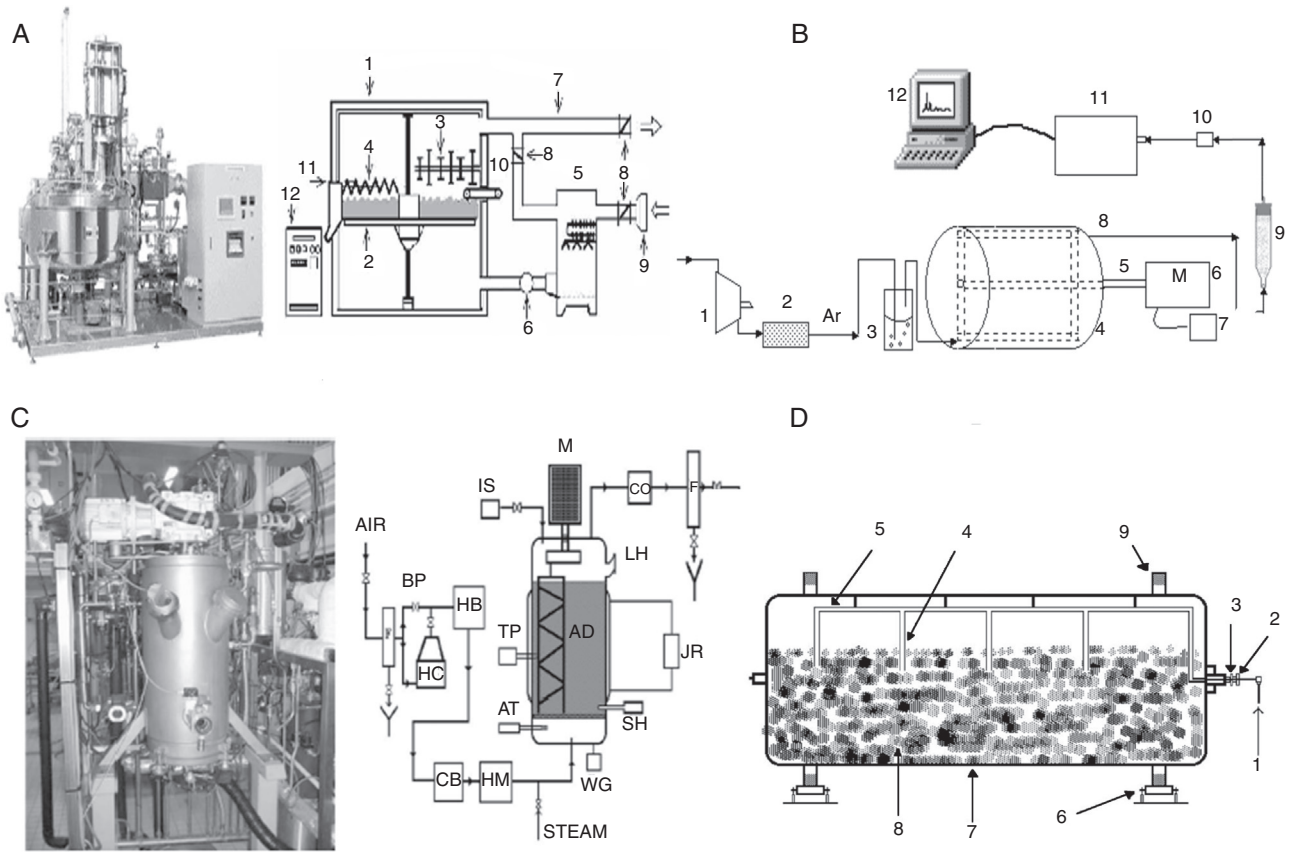


Figure 2 (A) Koji making equipment: (1) Koji room, (2) rotating perforated table, (3) turning machine, (4, 11) screw and machine for unloading, (5) air conditioner, (6) fan, (7) air outlet, (8) dampers (9) air filter, (10) machine for filling, (12) control board. (B) Schema horizontal drum: (1) compressor, (2) Air filter, (3) humidifier, (4) horizontal drum, (5) stirrer, (6) motor, (7) speed controller, (8) air discharge, (9) silica gel columns, (10) element name (11) gas chromatograph (12) computer. (C) Sterile bioreactor developed by the National Institute of Agronomic Research in Dijon (F) Air filter, (HC) humidification chamber, (HB) heating battery, (BP) by-pass, (CB) cooling battery, (HM) probe for air relative humidity measurement, (TP) probe for medium temperature measurement, (WG) weight gauges, (SH) sterile sample handling, (JR) water temperature regulation in the double jacket, (AD) planetary agitation device, (M) motor for agitation, (IS) sterile system for adding inoculum and solutions, (CO) water air condenser. (D) Rotating drum bioreactor. (1) Air-inlet, (2) rotating joint, (3) coupling, (4) air nozzles, (5) air line, (6) rollers, (7) rotating drum, (8) solid medium, (9) rim.
Sources: Modified from Durand (2003), Singhania et al. (2009) and Spier et al. (2011).

experimental results. A large number of patents and publications are available on how to design, operate and scale-up SSF bioreactors. Difficulties to scale-up are related to the intense heat generation and heterogeneity of the system. The microbial growth under aerobic conditions results in considerable heat production that causes a fast increase of temperature. This effect is undesirable especially in some biotechnological processes of heat sensible products or enzymes that can be heat-denatured. The water lost by evaporation has to be in many cases replenished, and this can lead to undesirable local increase in water activity during static processing. Several bioreactor designs have been developed in an attempt to combat these problems, but only a few have been used at large-scale, and information available about their performance is increasing in the form of original research articles as well as reviews (Singhania et al., 2009; Spier et al., 2011; Thomas et al., 2013).

From the above studies, it could be concluded that efforts have been made to modify the known design of SSF bioreactors. New information has been generated on the impact of process parameters such as aeration to better define the heat and mass transfer effects. Thus, while the basic designs of the bioreactors have remained the same, a lot new information has been generated on their modification, or on other processing aspects.

Recent patents and innovations

Patents can be used as a source of information about all sorts of technologies. When a technology is patented, specific knowledge about its novelty, inventiveness and industrial applications must be disclosed. Besides, it is possible to infer indirect information about it, such as its origin, history and state of development. Due to the requirements for a patent to be granted, it is possible to say that a patent document has the newest information compared to the state of the art. On top of that, it is presumable that a patented invention

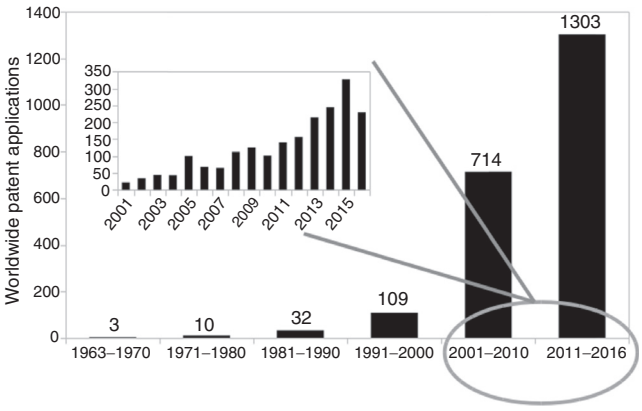


Figure 3 Evolution of patent applications related to SSF technologies, since 1963.

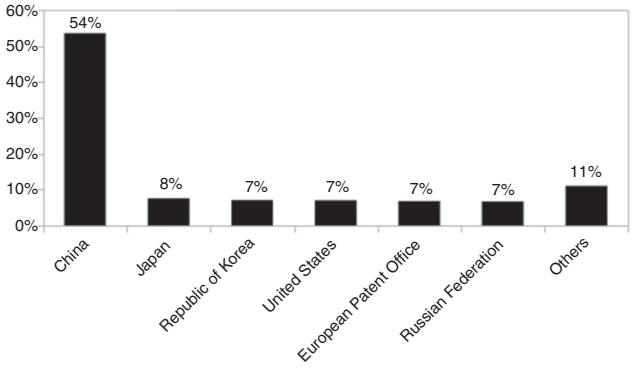


Figure 4 Distribution of SSF-related patent applications between the countries that contribute more to this technology development.

have a well-defined industrial application, and is nearing a commercially availability. When combined with complementary data, they provide a basis for a broad analysis of various dimensions of innovations, as the role of intellectual property, of economic performance, entrepreneurship and on search for links in science and technological development (Ferreira da Costa, Soccol, & Soccol, 2016; OECD, 2009; WTO, 1994). In this context, it is important to analyze any specific technology using this data.

The first patented invention regarding SSF was filed in 1962 by Riker Laboratories, Inc., today subsidiary of 3M Company. This invention aimed to produce a pyrogen-free penicillinase and was used in injection therapy for combating allergic sensitivity to penicillin (Riker, 1962). According to Pandey (2003) this technology was not used in the western countries until the 1940s, due to the development and wide use of submerged fermentation. SSF only became subject of study from 1950 on, on a slow pace. It was after the end of the 1990s that the interest in this technology boomed. Almost 93% of the total worldwide patent applications regarding SSF (2178) were filed after 2001, as illustrated in Fig. 3. The trend from 2001 to 2016 is highlighted on the chart. It is evident the raise in the number of applications is continuous. There has been no considerable decrease in such filings, since 2001. No peak has been reached yet, and there is no sign of a change of pace, as the number of patent applications is still trending upwards. The apparent decrease in 2016, when compared to 2015, may be explained by the fact that the year is yet to end and the 18-month secrecy period of every patent application. The latter may also be responsible for an underestimation of 2015's numbers, which would help to steep down the growth curve.

Fig. 4 presents the distribution of SSF related patent applications, filed through the Patent Cooperation Treaty (PCT), a system used to ease international applications. Therefore, the presented data ignores resident applications and may underestimate the relevance of some countries that traditionally does not file patents overseas.

China is the country with more patent applications in the world, with a large margin to Japan, South Korea, United States, European Union and Russia. This is probably due to the fact that this technology has only recently attracted interest from western scientists and industries, due to its applicability in production of several products using industrial residues as substrate. Also, SSF has been used in China for food and beverage production for thousands of years, and continues to be relevant to date. Over 80% of fermented foods and beverages, such as soy sauce, vinegar, distilled spirits, sufu, lobster sauce and mushrooms, produced in China are made via SSF (Liu et al., 2004; Wei, 2001).

Brazil, as one of the most important agricultural countries in the world, carries a strong potential for SSF due to its high availability of solid residues, commonly used as substrate in this kind of fermentation. It does not appear in the worldwide ranking, but it has been filing a considerable number of patents in its local patent office (173). It is important to mention a specific group in Curitiba that has contributed immensely to the development of SSF-related technologies in Brazil: the Department of Bioprocess Engineering and Biotechnology in *Universidade Federal do Parana* has been one of the most prolific research group in that area, filing patents since the end of the 1990s, being strong in transforming agro-industrial residues in high-value products. Relevance of said group was already discussed by Soccol and Vandenberghe (2003).

A patent, when filed, receives at least one International Patent Classification (IPC), which may refer to its function and/or its application. A patent may receive more than one IPC and, usually, this classification considers the additional information to the state of the art, including the invention's novelty, inventiveness and industrial application (WIPO, 2016). Through the analysis of this data the patent applications were segmented according to their received IPC, as presented in Fig. 5. SSF-related patents are classified in many different classes, but most of them regard food and beverage technologies. Over 30% of the patents were classified as novel to the food or beverage industry. Those included fermented alcoholic and non-alcoholic beverages, such as milk, wine, beer, vinegar, and the modification of foods, comprising most oriental fermented foods. Several patents regards the development and production of animal feed. Most of them use fermented residues to increase the quality of such products.

It is important to notice the number of patents regarding development and/or modifications made to bioreactors. This trend is something already anticipated and discussed by Singhania et al. (2009) to improve SSF efficiency and help its

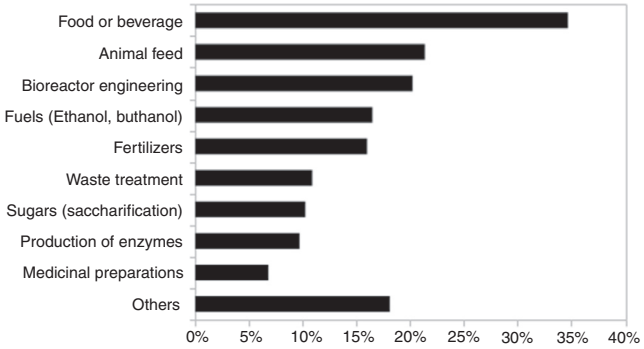


Figure 5 Patent applications classified according to their function or application.

scale-up process, which is pointed as one of the most important drawbacks of this technology to make it commercially feasible.

Other interesting areas receiving attention are fuels production (mainly ethanol and butanol), waste treatment, production of enzymes and saccharification. A lot of inventions that received this IPC aimed to produce biofuels from lignocellulosic residues, a technology that comprises several diverse processes, such as biomass treatment (waste treatment) to produce fermentable sugars (saccharification), enzymatic hydrolysis of cellulose (production of enzymes) and fermentation of sugars (polysaccharides, such as cellulose, or monosaccharides, such as glucose and xylose).

Production of enzymes is a well-known application of SSF. Production of phytase, amylase, inulinase, cellulase, protease, alpha-galactosidase, lipase, tannase, laccase, chitinase, l-glutaminase, lipase was widely studied and reviewed (Singhania et al., 2009). Production of fertilizers and pharmaceuticals, mainly antibiotics, also appear constantly in recent patent and inventions.

In order to assess the technologies that have been receiving most attention in the past 10 years, the most cited patents regarding SSF were reviewed.

Brown et al. (2005) describes a process for production of recombinant enzymes, including cellulase, endoglucanase, cellobiohydrolase and beta-glucosidase with cellulolytic activity, in order to treat cellulosic material, such as agricultural of forestry residue, solid waste, waste paper, or pulp and paper mill residue, or corn stover. The invention also comprises a saccharification and fermentation process, whereas the latter is made via SSF of the treated biomass, with the enzymes produced in the previous step. Product of this fermentation may be several, including alcohol, organic acid, ketone, amino acid, or gas. The main novelty of this patent resides on the amino acid sequences of the produced enzymes, alongside with the nucleotide sequences to translate them in recombinant microorganisms. Several microorganisms comprising these sequences are also claimed by the patent. They describe the production process of the enzymes, adding several applications and examples of use. Following the same pattern, Lombard (2001), Fukuyama et al. (2006), Vlasenko, Cherry, and Xu (2005), Berka and Cherry (2005), Boerge and Lena (2007), Krogh and Harris (2007) and Huang et al. (2010) describe different processes to perform a simultaneous saccharification and SSF process to produce ethanol from lignocellulosic materials. The main novelty of those inventions vary widely, from the hydrolysis of hemicellulose, removal of lignin and, mainly, the enzymes produced.

Suryanarayan, Mazumdar, and Mazumdar (2000) presents a modular bioreactor for cultivating microorganisms in solid medium. The base modulus contains communicating channels that are used to control several parameters of the fermentation, such as temperature and aeration. Other moduli may be stacked on top of each other, independently, and may be individually controlled. The bioreactor is closed to avoid contamination and comprises an agitation system. As the bioreactor is modular, it is totally adjustable and easy to disassemble. In the patent several examples of application are described. The modular aspect of this bioreactor is considered as the main novelty of this invention. Other modular bioreactors are presented in patents from Gorwalla and Kulkarni (2010) and Lueth and Wismar (2005).

An automatic chain-belt-type bioreactor for SSF is described by Lang and Zhang (2010). It is a sequential reactor, with the inoculating tank being connected with the fermentation reactor, through a spiral transmitter, which is noted as the main novelty of this apparatus. The transmission and withdrawal of materials are done automatically, so that the input to the second fermenter receives the output from the first one (inoculating tank). Patent Hoelker, Janssen, and Lenz (2004) also presents a chain-belt-type fermenter for SSF.

Most recent patent applications regarding bioreactor engineering have been focusing on improved controlling systems, stirring apparatus and adaptations for continuous cultures, including connections with downstream processes (Alitalo, Aura, & Niskanen, 2016; Hou et al., 2016; Kim, Liu, & Zhang, 2016; Lai, Xue, & Yang, 2016).

A method for producing organic fertilizer through anaerobic fermentation of solid waste, via SSF, is claimed by Du, Wang, Wang, Xu, and Zhao (2009). The invention comprises the preparation of different solid wastes, comprising steps for mixing it and regulating water content. Acidic and anaerobic fermentations are described in this patent. The main goal of the invention is to produce humic acid granule fertilizer.

As stated above, several patents regarding SSF are useful for food and beverage production or improvement. The products are very diverse, including vinegar (Cao, 2014; Li, 2009; Wang, Gao, & Yao, 2006), soy sauce and Koji (Lim, Ng, Heyland, & Dac, 1999; Liu, Wu, Yang, & Zhou, 2009; Yu, 2011), wines and spirits (Ao et al., 2009; Huang, Ji, Li, & Wang, 2009), food additives (Chen & Zhuang, 2008; Gao, Lu, & Yan, 2013; Sobol & Sobol, 2003), cereals (Jiang, Wang, Jiang, & Zhu, 2011; Sun, 2007). More recently, focus has been on technologies for production of foods and beverages with medicinal properties, such as antioxidant activity, lowering blood fat, helping digestion, promoting better blood circulation, among others (Cheng, Cheng, et al., 2016, Cheng, Fu, et al., 2016; Feng, 2016; Hu et al., 2016; Liu, Song, et al., 2016).

Conclusions

Solid-state fermentation (SSF) is an alternative fermentation technique whose characteristics allow the re-use

of agro-industrial and/or sub-products as substrate support for biotechnological production of low to high value biomolecules. It is very well stablished for certain traditional processes such as fermented food in the oriental countries. As it presents various advantages for certain processes, it still attracts much attention by many researchers worldwide. It is not surprising that a technology so elegantly simple continues to raise attention of scientists and industries around the globe, as shown by the patent data herein. As its potentials and applications are extremely diverse, there are important drawbacks yet to be solved, and there is no reason for a decrease in patent applications in the foreseeable future. The potentialities and advantages of SSF must be evaluated for each process. However, it is clear that some limitations for the scale-up are still observed. In this case, the choice of the microorganism, substrate/support and bioreactor are predominant and, of course, the economic viability depends on a careful comparison of SSF and submerged fermentation processes.

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