



Solid-state fermentation technology and innovation for the production of agricultural and animal feed bioproducts

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Abstract

It has now passed more than forty years since solid-state fermentation (SSF) research developments have gained importance for the scientific community. After so many years, numerous processes and equipment for SSF were studied and designed focusing on the production of different commercially relevant bioproducts such as enzymes, fermented food, such as Chinese *daqu* and *koji*, organic acids, pigments, phenolic compounds, aromas, biosorbents and so many others. However, no review paper has been focused yet specifically on agricultural and animal feed bioproducts obtained through SSF techniques. This review comprises the description of agricultural sub-products that have been employed in most important developed processes concerning the production of animal feed products and agricultural products such as spores, probiotics, biofungicides, bioinsecticides and other biopesticides, biofertilizers and plant growth hormones. Major designed SSF bioreactors are also described and the most important related cases of successful employment of the technique are reported. Finally, a summary of patents and innovations regarding SSF products and processes in this area is presented, showing that the main involved countries are China, South Korea, India and the USA. It is clear that the interest in this theme is increasing and that scientific and technological developments are still needed.

Keywords Alternative sub-products · Solid-state fermentation bioreactors · Animal feed · Agricultural bioproducts · Probiotics · Patents

Introduction

Solid-state fermentation (SSF) is a process where there is a porous solid substrate or support for the growth of microorganisms, with a continuous gas phase. It is arguably the most natural condition for the growth of microorganisms whose natural habitats are solid materials, such as plant and rock surfaces, soils and decomposing organic matter such as leaves, bark and wood. In nature, solid carbon-rich substrates are much more common than liquid media—and therefore,

SSF processes can match the natural physiology of microorganisms: a generally lower water activity than in liquid media, low to zero shear stress and direct contact with gas phases [1–5].

The history of solid substrate fermentation is rooted in ancient processes such as dough and cheese fermentations. However, following our understanding of a granular solid and a continuous liquid phase, the prototypical SSF process is the *koji* fermentation, dating back to at least 300 BC—the first mention of *Qu*, a Chinese ancestral of red rice *koji* [6]. *Koji* is a steamed cereal (typically wheat or rice) inoculated with spores or a previously fermented batch of a filamentous fungus, most commonly *Aspergillus oryzae* [7]. The resulting mash has a very high enzymatic activity and is industrially used for the production of sake, soy sauce or vinegar.

The process produces high concentrations of hydrolases, especially amylases and was extensively investigated for enzyme and citric acid production before liquid fermentation took over [5]. Both because of the high titer of bioproducts,

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and the mixed enzymatic cocktails that can be produced, there is active ongoing research on the subject [8–10]. A resurgence of SSF occurred because of its capability for the value addition of abundant agroindustry residual biomass [11, 12], on par with the modern concept of bioeconomy and circular processes. Not only the use of agro-industrial residues provides alternative substrates but also can serve agriculture directly, with the production of inoculants and bioactive secondary metabolites [4].

To better understand SSF, it is useful to see which aspects of it differ from liquid fermentation and semisolid fermentation (Table 1).

SmF processes have advantages related to instrumentation and control (monitoring of pH, dissolved oxygen, temperature, concentration of water-soluble molecules), separation of biomass after fermentation, mixing, aeration and scale-up [13]. However, solid medium is the natural habitat of innumerable microorganisms, mainly fungi, which is the main advantage of SSF. Besides, it demands less energy for sterilization, it is less susceptible to bacterial contamination and substrate inhibition, and it promotes higher final concentration of products. Another advantage is that it allows the use of solid agro-industrial wastes

as substrate in their natural form and facilitates the solid waste management, besides lesser wastewater production with consequent less environmental impacts [14].

It is widely recognized that SSF has enormous potential, but is technically less developed than SmF, at least in Western countries. However, as pointed out, differentiating microorganisms may be best produced in SSF, as is the case in spore production. This can be observed in specialty products such as agricultural inoculants and secondary metabolites. However, despite the important corpus of research in SSF, there are no reports that describe agroindustry-relevant products; this review carefully curated recent research on the topic, which is exceptionally relevant to the sustainable growth of the global crop and animal production. Besides, it gives a view about the main employed bioreactors, and recent developed patents and innovations in this area.

Table 1 Key aspects of solid, semisolid and liquid fermentation

| Characteristic | Solid-state fermentation | Semisolid fermentation | Submerged fermentation |
|--|---|---|--|
| Common acronym | SSF | | SmF |
| Synonym | Solid substrate fermentation | | Liquid fermentation |
| Typical water content (mass/mass) | 40–70% | Lower than 30–40% | Lower than 30% |
| Typical water activity (a_w) | Usually below 0.95 | Above 0.95 | Above 0.95 |
| Agitation, anaerobic systems | None | Mild, continuous, to avoid settling | Continuous, by natural convection or mild mechanical agitation |
| Agitation, aerobic systems | Typical: None Possible: Periodic, low intensity | Continuous, low intensity | Continuous, mild (pneumatic or with agitators) to high intensity |
| Gas exchange | With pre-humidified air, direct or semi-direct (gas > cells or gas > substrate > cells) | With air, indirect contact (bubbles > liquid > cells) | With air, indirect contact (bubbles > liquid > cells) |
| Temperature control and heat exchange | Less strict control, heat exchange, mainly with the gas | Strict control, exchange with gas and walls | Strict control, exchange with gas, walls and coils |
| A_w control and evaporative loss reduction | Low control; gas humidification, water sparging | Strict control, water addition | Strict control, water addition |
| pH and medium composition control | Unusual, difficult | Direct measurement, acid/base/nutrients addition | Direct measurement, acid/base/nutrients addition |
| Medium preparation | Nutrient amendment, sterilization, solid manipulation, slow cooling | | Total formulation, sterilization, controlled cooling |
| Substrate concentration | 40–70% of the mass | | < 20% |
| Process contamination | Reduced because of the low water activity | | Critical, controlled with antibiotics or strict control |
| Product extraction | Favorable because of o high concentration | | Must concentrate large fermentation volumes |
| Scale-up | Complex | | Relatively simple |

Agro-industrial sub-products as potential substrate/supports for SSF

Typical substrates for SSF come from forest or agro-industrial wastes generated in large quantities. In general, part of it is used for energy cogeneration, while the other part is underutilized and can often cause environmental problems [15]. Their average composition is quite variable but is mostly composed of fibrous materials (lignocellulosic) or bran, which in some cases may be rich in starch, lipids and other organic compounds [16]. The characterization of some of the most generally used substrates for agricultural and animal feed bioproduct through SSF is presented in Table 2.

Solid-state fermentation processes may be carried out using inert supports, such as polyurethane foam,

polystyrene, vermiculite, perlite, amberlite and clay granules among others that must be supplemented for microorganisms' growth [17, 18]. However, most substrates originated from agricultural wastes act not only as physical support, but also as a carbon and energy source [19]. In this case, these alternative substrates are then supplemented with nitrogen source, micronutrients, such as ions, salts and vitamins. In addition, chemical composition, other characteristics of solid substrate are fundamental such as particle size, surface area, porosity and crystallinity. These physical characteristics vary not only with the chosen substrate, but strongly depend on the pre-processing and processing steps. Finally, and perhaps the most important is the substrate cost and availability [15]. Depending on the target necessity, a complete process must be defined and designed, including the choice of

Table 2 Physicochemical composition of some important substrates for SSF (in dry basis, except when otherwise stated)

| Substrate | Protein (%) | Carbo-hydrates (%) | Lipids (%) | Ash (%) | Fiber (%) | Other | References |
|-------------------|-------------|--------------------|------------|---------|-----------------|--|------------|
| Soybeanmeal | 46 | 15 | 1 | 6 | 22 | | [20] |
| Canola meal | 36 | 11 | 4 | 7 | 32 | | [20] |
| Rapeseedmeal | 34 | NIA | 1 | 7 | 9 | | [21] |
| Cornbran | 13 | 46 | 13 | 3 | 16 | Moisture: 9% | [22] |
| Rice bran | 16 | 40 | 15 | 8 | 7 | | [23] |
| Wheatbran | 17 | NIA | 15 | 6 | 10 | Neutral detergent fiber: 45–51%; acid detergent fiber: 13–39%; lignin: 3–11%; starch: 23%; total sugars: 7%; | [24] |
| Apple pomace | 2 | 85 | 2 | 2 | 30 ^a | Moisture: 9% Total dietary fiber: 30% ^a ; total sugars: 54; Starch: 6% | [25] |
| Orange pomace | 6 | 78 | 2 | 4 | 40 ^b | Moisture: 11%; total dietary fiber: 40% ^b ; total sugars: 25%; starch: 3% | [25] |
| Cassava bagasse | 1 | 40–75 | 1 | 1–12 | 15–51 | Cellulose: 4–11%; hemicellulose: 4–8%; lignin: 1% | [26] |
| Sugarcane bagasse | NIA | NIA | NIA | 2 | 86 | Klason lignin: 18%; acid soluble lignin: 2%; holocellulose: 76% | [27] |
| Coffeehusk | 8 | NIA | 3 | NIA | 72 | Soluble dietary fiber: 12%; insoluble dietary fiber: 60% | [28] |
| Corncob | 3 | NIA | 1 | 2 | 46 ^c | Crude fiber: 46% ^c ; neutral detergent fiber: 77%; acid detergent fiber: 39%; lignin: 10% | [24] |
| Rapeseedstraw | 2 | NIA | 2 | 2 | 86 | Hemicellulose: 15%; cellulose: 49%; acid soluble lignin: 18%; acid insoluble lignin: 4% | [29] |
| Rice straw | 4 | NIA | 1 | 18 | 35 ^d | Crude fiber: 35% ^d ; neutral detergent fiber: 69%; acid detergent fiber: 42%; lignin: 5% | [24] |
| Wheatstraw | 4 | NIA | 1 | 9 | 41 ^e | Crude fiber: 41% ^e ; neutral detergent fiber: 77%; acid detergent fiber: 50–54%; lignin: 7–23%; cellulose: 34–40%; hemicellulose: 21–35%; starch: 1%; total sugars 1%; silica and silicates: 5% | [24] |

All the values in the table are rounded. NIA: no information available in the respective reference

^aReference [25] reported apple pomace total dietary fiber as 30%

^bReference [25] reported orange pomace total dietary fiber as 40%

^cReference [24] reported corn cob crude fiber as 46%

^dReference [24] reported rice straw crude fiber as 35%

^eReference [24] reported wheat straw crude fiber as 41%

the proper microorganism to be used, the balanced substrate to be prepared, the proper process variables and performance to be controlled during the SSF including temperature, air flow and support/substrate compaction, among others.

Solid-state fermentation bioreactors design

Even if the Chinese employed SSF techniques for food fermentation since the antiquity, only in the eighties this technique regained interest by the scientific community when some researchers [30] started to work with packed-bed columns. The so-called Raimbault columns were then increasingly used for laboratory-scale studies. Afterwards, some SSF bioreactors models were developed and classified based on the employed mixing system: static bioreactors (packed-bed columns, perforated trays) or stirred bioreactor (horizontal drum, stirred drum and others), which are classified according to the type of aeration [15, 31, 32] or mixing system [14]. SSF bioreactors have their own advantages and disadvantages, even so the necessity to develop novel bioreactors with better design appeared with some existent limitations and the demand of new processes. Durand [32] reported different designs of SSF bioreactors with the description of some characteristics of the most employed equipment. Each bioreactor was designed and operated depending on the process and employed substrate, where composition, size, strength, porosity and water holding capacity are important parameters to observe.

Solid-state fermentation occurs in the absence of free water and, thus, some details must be considered in bioreactor design including the techniques of inoculation, substrate type, sampling and mass transfer systems, type of aeration, agitation, shaking arrangement and monitoring and control of various parameters [33]. Besides, other factors such as materials and methods of construction of the fermentation vessel, ability to withstand pressure, sterilization, process variables and extent of control required could lead to the development of reliable commercial fermentation equipment.

The type of microorganism also affects the performance of the bioreactor. Filamentous fungi are generally very well adapted to this fermentation technique. However, the type of fungi hyphae may influence the agitation (static, intermittent or continuous). Aeration must also be defined, which can occur by diffusion or as forced aeration). Some developed SSF types bioreactors, which are classified according to their static (non-agitated) or agitated profile, are presented as follows.

Static bioreactors

The absence of agitation is the major characteristic of the static bioreactors, which is important in SSF processes where the rupture of filamentous fungi would be prejudicial [32]. Some models of static bioreactors are available for SSF and for different scales. This group of bioreactors includes Erlenmeyer flasks, perforated trays, packed-bed bioreactors or Raimbault columns, the PLAFRACTOR and others. The simplicity and the operability of these bioreactors are great advantages. Erlenmeyer flasks are made of glass, low cost and easy of handle, allowing their employment at laboratory scale for preliminary studies and processes' optimization. Aeration occurs by diffusion through cotton plugs that are used to close the flasks. Different types of static bioreactors for SSF are presented in Singhanian et al. [14] and Soccol et al. [15].

The Raimbault columns, packed-bed or fixed-bed bioreactors [30] are static systems with forced aeration, which are usually employed at laboratory scale (Fig. 1). The columns are filled with the solid substrate/supports that are impregnated with nutritive solution at a defined initial humidity and inoculated. The column bioreactors are connected to air bubblers and positioned into a water bath that allows temperature control. Adjusted flow of saturated air passes through the columns, which is controlled by a flowmeter at the outlet side. With forced aeration, some inevitable temperature gradients are minimized, due to the convection promoted by the passage of air through the reactor and the efficient removal of heat. Besides, these bioreactors allow the study of the influence of forced aeration on microorganism's growth and metabolism and biomolecules' production through the evaluation of consumed O_2 and produced CO_2 (Fig. 1a). The elimination of CO_2 from metabolic reactions occurs, which is an advantage for some processes. The system is closed providing less contamination. Moreover, the same bioreactor can be used for both fermentation and extraction procedures of the final product [14, 15]. The problem of this bioreactors is linked to the reduction of bed's porosity with the progress of fermentation and microorganisms' growth.

A pre-pilot scale design of packed-bed bioreactor was developed. In this case, substrate is supported by a sieve through which the forced air passes (Fig. 1b). Temperature, airflow rate, addition of water and agitation can be controlled during SSF process. It can be placed in a clean room where the bioreactor can be pasteurized in situ by steam generated by the water-bath used for the air humidification. It is a simple model of bioreactor with high medium capacity. If the process needs homogenization, the bioreactor can be adapted with a mixing device coupled with forced aeration [14, 15].

Tray bioreactors are simple systems consisted of perforated trays, which are made by wood or stainless steel, where substrate is disposed in thin layers (from 5 to 15 cm)

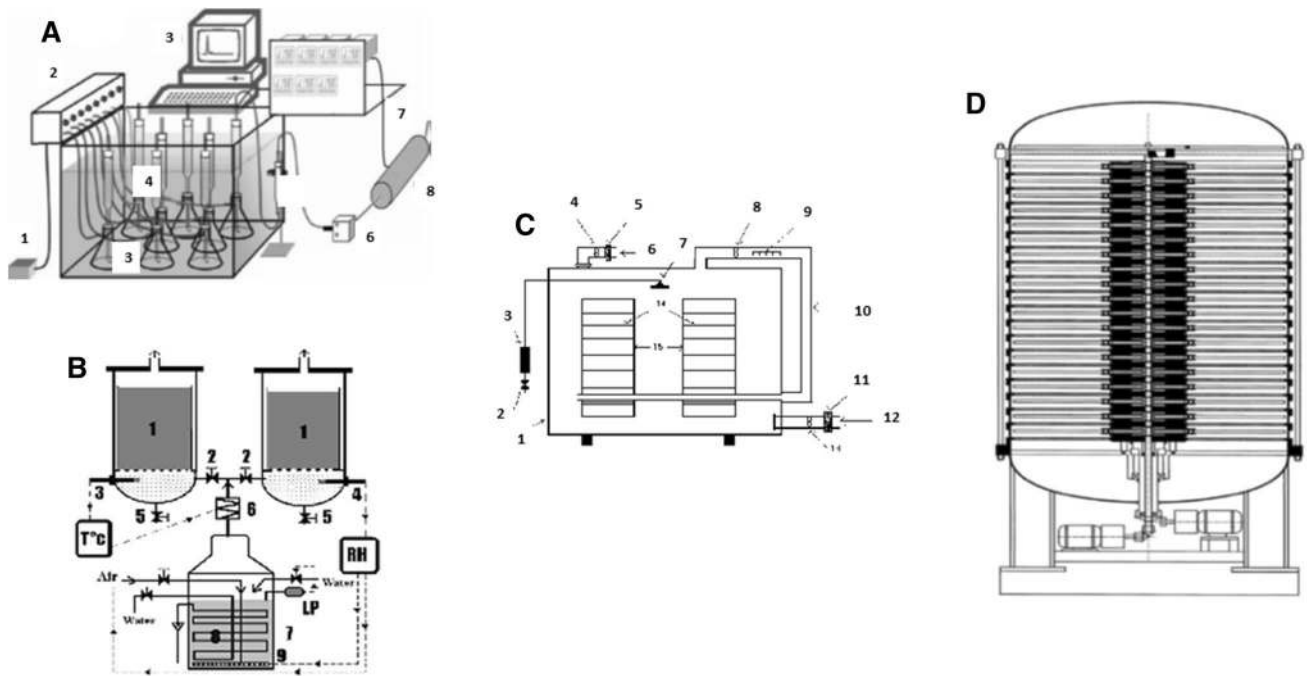


Fig. 1 **a** Laboratory-scale fixed-bed bioreactors apparatus for solid-state fermentation: (1) air pump; (2) air distribution system; (3) humidifiers; (4) fermentation columns immersed in a water bath with controlled temperature; reactor; (5) filter; (6) flow sensor; (7) controllers display; (8) computer with data acquisition and control software; (9) cylindrical sensor base, where the following sensors are installed: CO₂ and O₂, humidity and outlet temperature; **b** unmixed bioreac-

tors 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; **c** perforated trays bioreactor; **d** schematic representation of PLAFRATOR bioreactor showing multiple modules stacked vertically. Sources: modified from [15, 32, 34]

(Fig. 1c). This system is largely employed in Eastern countries for food fermentation. Trays are arranged in a chamber with controlled temperature and humidity. Trays are arranged with a space between them to allow the aeration that occurs by convection. High scale processes can easily employ this bioreactor system. However, large areas are needed for operations. It requires intensive labour and there is a higher degree of contamination because it involves non-sterile processes. Oxygen transfer limitations are also another problem caused by the formation of the mycelium that changes of the porosity and affecting diffusivity. Higher substrate layers create higher O₂ gradients. Another model is the PLAFRATOR (Fig. 1d) a modular design patented by Biocon Ltd. claimed for a self-contained SSF device that combined all fermentation operations i.e., sterilization, inoculation, cultivation, extraction and post-extraction treatment, in a single unit. It was validated for sterile production of proteases, cyclosporine, amylases and lovastatin [15, 32, 34].

Agitated bioreactors

SSF bioreactors are also constructed with agitation devices, which can work intermittently or continuously [15, 19, 32] (Fig. 2). Higher homogeneity of the solid medium and better

mass transfer and aeration are then expected in agitated system. Agitated bioreactors can be fabricated with or without a water jacket for temperature control. The schematic system of horizontal drum bioreactors is shown in Fig. 2a. The agitation in this type of reactor can be continuous or sporadic. Depending on agitation intensity, there may happen shear problems and damage of fungal mycelium structure [15, 32].

Rotating drum bioreactors (RDB) consist of horizontal cylinders where mixing occurs by tipping, providing a gentle and uniform mixing. Besides, there can be baffles inside the rotating drum that may facilitate mixing process that is less efficient than with a paddle mixer (Fig. 2b). RDBs with air circulation and continuous mixing are commonly used in laboratory or pilot scale processes. According to Durand [15, 32], the largest cited RDB was a 200-L stainless steel bioreactor with a capacity of 10 kg. It was used for kinetic studies of *Rhizopus* cultivation with wheat bran as substrate.

Another example of SSF bioreactor is the equipment for Koji production, manufactured by Fujiwara in Japan (Fig. 2c). This type of design is widely used in Asian countries. This non-sterile bioreactor is equipped with controls for process parameters (air-inlet temperature, air flow rate and agitation period). Different working volumes are available, but a maximum layer thickness of

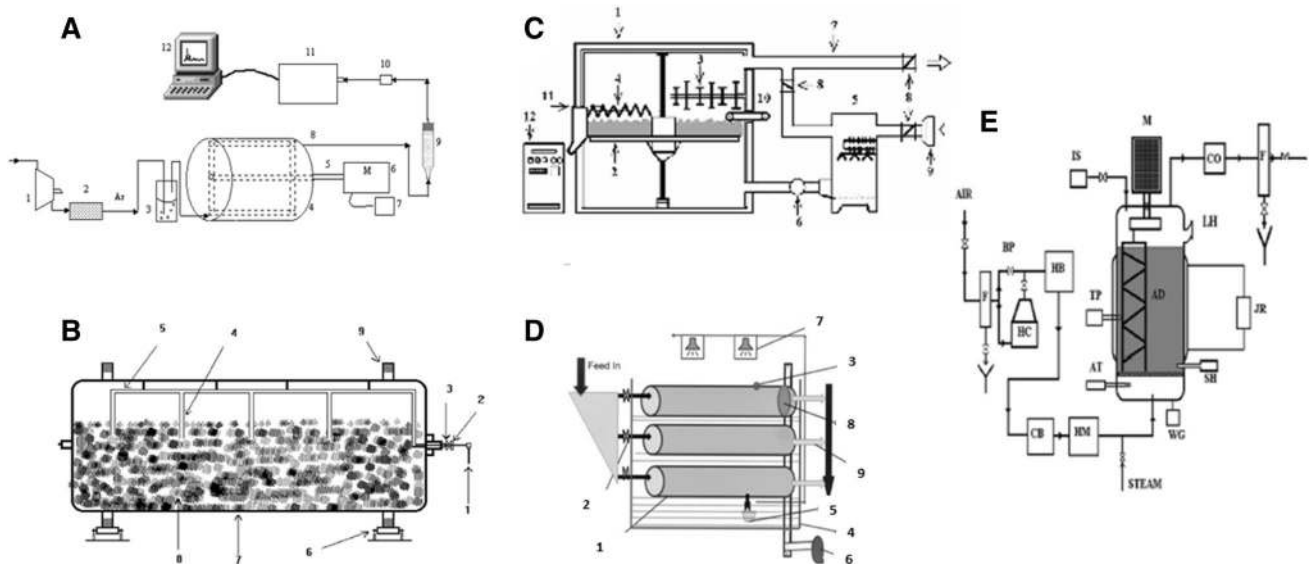


Fig. 2 **a** Schema of horizontal drum: (1) compressor, (2) air filter, (3) humidifier, (4) horizontal drum, (5) stirrer, (6) motor, (7) speed controller, (8) air discharge, (9) silica gel columns, (10) (11) gas chromatograph (12) computer; **b** rotating drum bioreactor: (1) air-inlet, (2) rotating joint, (3) coupling, (4) air nozzles, (5) air line, (6) rollers, (7) rotating drum, (8) solid medium, (9) rim; **c** 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; **d** multi-drum bioreactor: (1) fiber column, (2) control valve for feed input, (3), temperature sensor, (4) water in the tank, (5)

sample collector, (6) rotating arrangement to rotate the columns, (7) water sprayers, (8) mesh, (9) product for purification; **e** 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. Sources: modified from [14, 15, 32]

50 cm is used. Substrate is prepared and inoculated in other equipment before filling the reactor [14, 15, 32].

An interesting new design for SSF processes has been projected with multiple individual rotating drum bioreactors, which are arranged vertically with independent inlets. So, each individual unit can be used separately (Fig. 2d). Aeration is maintained or not in the bioreactor, and it is continuously cooled using a sprinkler overhead for temperature control. The bioreactor is made of acrylic polymer tubes that are transparent, flexible, non-corrosive and temperature resistant. It has an average working capacity of around 20 kg with the following specifications: diameter of the tube is 15 cm, the length of each tube is 100–150 cm, baffle spacing is $\frac{1}{4}$ tube diameter, and tubular volume is 50–70% of total volume [31].

A 50-L bed bioreactor was patented by Durand [32]. This reactor has a planetary mixing device (Fig. 2e) with automatic control for sterilization of the bioreactor and the medium, control of process parameters during fermentation and data acquisition.

Agriculture bioproducts produced in SSF bioreactors

There is a great potential of SSF bioreactors to be applied in agricultural bioproducts from alternative substrates. In fact, this technique is very adapted to the production of these molecules with a high efficacy. Some examples of bioreactors employed in the production of agricultural and animal feed bioproducts are presented in Table 3.

Reports of the use of SSF bioreactors agricultural and animal feedbiomolecules' production, such as plant growth hormones (gibberellic acid) and spores, showed that these processes are generally carried out in closed and aerated systems such as horizontal drum and packed-bed bioreactors or in open systems like tray bioreactors.

Gibberellic acid (GA₃) production was conducted by *Gibberella fujikuroi* in packed-bed column bioreactors. The solid medium consisted of coffee husk (pretreated with alkali solution), mixed with cassava bagasse (7:3 dry weight basis), with a substrate initial pH of 5.2 and moisture of 77%. The

Table 3 Some examples of agricultural and animal feed bioproducts produced in SSF bioreactors

| Type of Bioreactor | Aeration system | Agitation | Microorganism | Substrate | Product | References |
|--|-----------------------|--------------|-------------------------------|--|------------------|------------|
| Horizontal drum | Forced aeration | Intermittent | <i>Gibberella fujikuroi</i> | Coffee husks | Gibberellic acid | [35] |
| Intermittent mixed | Forced aeration | Intermittent | <i>Clonostachys roses</i> | Wheat bran–maize meal | Spores | [36] |
| Modified tray | Aeration by diffusion | Static | <i>Clonostachys roses</i> | Wheat bran–maize meal | Spores | [36] |
| Packed bed | Forced aeration | Static | <i>Bacillus licheniformis</i> | Rice straw powder | Spores | [37] |
| Packed bed | Forced aeration | Static | <i>Bacillus atrophaeus</i> | Sugarcane bagasse + soybean molasses | Spores | [38] |
| Polyethylene bags; Erlenmeyer flasks | Aeration by diffusion | Static | <i>Bacillus atrophaeus</i> | Sugarcane bagasse + soybean molasses | Spores | [38] |
| Solid-state bioreactor with honey loading device (HDL) | Forced aeration | – | <i>Bacillus cereus</i> DM 423 | Wheat bran–rice bran–soybean cake powder | Spores | [39] |
| Tray | Aeration by diffusion | Static | <i>Beauveria bassiana</i> | Rice | Spores | [40] |

preinoculated substrate was packed in glass columns, which were connected to forced aeration of 0.24 L of air h⁻¹ g⁻¹ dry matter⁻¹ for the first 3 days, and 0.72 L of air h⁻¹ g⁻¹ dry matter⁻¹ for the remaining period. The columns were connected to a gas chromatograph where the exit gas was analyzed. Respirometric data were employed to determine a logarithmic correlation between accumulated CO₂ and biomass production. The maximum specific growth rate (μ_m) was 0.052 h⁻¹ (between 24 and 48 h of fermentation). A production of 0.925 g of GA₃ kg of dry matter⁻¹ was achieved after 6 days of fermentation [35].

Spores production was conducted in trays [36, 40] and packed-bed bioreactors [37, 38] using different alternative substrates such as wheat bran, maize meal, rice straw and sugarcane bagasse with both fungal (*Beauveria bassiana* and *Clonostachys roses*) and bacterial (*Bacillus licheniformis*) strains. Sporulation reached better results in packed-bed bioreactor from 0.9 to 3.36 spores g dry matter probably due to forced aeration that is promoted in this type of equipment, which is the advantage of this model. Tray bioreactors are open systems where aeration occurs by diffusion with lower growth rates and risk of humidity lost and contamination.

An innovative SSF bioreactor was designed by Zhang et al. [36] for spores' production by *Clonostachys rosea* mutant strain CRM-16. The bioreactor differs from original tray bioreactors because it is ventilated at the top and the bottom and transparent, which allows light penetration at the top. In this case, compared to the traditional tray bioreactors, it provides higher growth and sporulation due to the larger exposed area. The bioreactor is composed of four frames (2.0 × 0.5 m for each), each one with a plastic mesh that can be loaded with 25 kg of solid culture medium. A high-density polyethylene membrane with appropriate surface porosity is employed to cover the top and the bottom of the tray and play an important role in reducing the risk of bacterial contamination. Two mixings were carried out during cultivation that resulted in a mass of new

sporulation surface, attaining 3.36 × 10¹⁰ spores g⁻¹ dry matter⁻¹. The sporulation was 10 times greater than that of traditional tray reactor with shorter period of fermentation, from 14–15 to 10–11 days. The new bioreactor showed great potential for spores production by *C. rosea* and other fungal biocontrol agents.

Examples of SSF bioproducts applied in animal feed and agriculture

Animal feed bioproducts

Bioproducts applied in animal feed can be produced by SSF preferably using a single substrate. The reason for that is the easier process control and quality of the fermented product before its addition (as additive) in the final product formulation [41]. Soybean meals are the most common used substrates, but many others are cited such as winery wastes, bagasses (mainly sugarcane and cassava), fruit peels and pulps [42]. A wide range of microorganisms are used as starter cultures, including yeasts (notably *Saccharomyces cerevisiae*), fungi (mainly *Aspergillus* sp.) and bacteria (especially *Bacillus* sp. and lactic acid bacteria). The improvements provided by SSF for animal feed products include, among others, the increase in protein content (both in quantity and quality), the reduction of anti-nutrient content (such as phytate), improvement of digestibility for animals (low crude fibers and/or polysaccharides content) and inhibition of pathogens such as *Salmonella* sp. (production of organic acids and/or other antimicrobial metabolites) [41].

Some examples of high-quality animal feed bioproducts produced by SSF using different substrates and microorganisms are presented in Table 4.

Table 4 Examples of SSF processes for animal feed production, with highlight for chosen substrates, microorganisms and the main improvement features for animal feed quality (adapted from Dai et al. [41])

| Substrate | Microorganism | Improvement for animal feed quality and/or animal health | Application | References |
|--|---|---|----------------|------------|
| Soybean meal | <i>Saccharomyces cerevisiae</i> , <i>Lactobacillus acidophilum</i> , <i>Enterococcus faecalis</i> , <i>Bifidobacterium bifidum</i> , <i>Bacillus licheniformis</i> , <i>Bacillus subtilis</i> | Inhibition of pathogens growth (<i>Escherichia coli</i> and <i>Salmonella aureus</i>) | Pig feed | [43] |
| Soybean meal | <i>Enterococcus faecium</i> | Removal of trypsin inhibitor, stachyose and raffinose | Pig feed | [44] |
| Soybean meal | <i>Lactobacillus plantarum</i> , <i>Bacillus subtilis</i> , <i>Saccharomyces cerevisiae</i> | Increase in crude protein and acid soluble protein; decrease of trypsin inhibitor, stachyose, raffinose and glycine | Pig feed | [45] |
| Soybean meal | <i>Saccharomyces cerevisiae</i> | Increase in total protein and aminoacids content, decrease in phytic acid and trypsin inhibitor; improvement in digestibility | Fish feed | [46] |
| Corn meal, soybean meal and wheat bran | <i>Bacillus subtilis</i> , <i>Enterococcus faecium</i> | Increase in total protein content, small peptides, aminoacids, ash and total phosphorous; decrease in antigen proteins content | Pig feed | [47] |
| Corn bran, corn cob, cassava peel, groundnut husk meal, moringa seed husk, palm kernel meal, rice bran, wheat bran | <i>Pleurotussajor-caju</i> | Increase in total protein and aminoacids content | Feedstock feed | [48] |
| Flaxseed cake | <i>Aspergillus niger</i> , <i>Candida utilis</i> | Increase in crude protein and calcium content and decrease in hydrocyanic acid level; increase in nutrients bioavailability for ducklings | Ducklings feed | [49] |
| Lupin meal | <i>Aspergillus niger</i> | Improvement of fish growth, feed performance and gut morphology | Fish feed | [50] |
| Rapeseed cake | Spontaneous fermentation | Reduction of phytate and glucosinolates | Turkey feed | [51] |

Table 4 (continued)

| Substrate | Microorganism | Improvement for animal feed quality and/or animal health | Application | References |
|--|--|---|---------------------------|------------|
| Rapeseed cake and wheat bran | <i>Aspergillusniger</i> | Increase in crude protein and acid soluble protein and ether extract content; decrease fiber and phytic acid content | Pig feed | [52, 53] |
| Rapeseed meal, sunflower meal, faba beans, wheat bran, potato pulp | Lactic acid bacteria from a commercial product | Increase in the solubility of protein and phosphorus | Pig and poultry feed | [54] |
| Wheat bran | White rot fungi (<i>Pleurotuseryngii</i>) | Increase in lignocellulolytic enzymes activity and in the expression of antioxidant molecules after the ingestion by broilers | Broiler chicken feed | [55] |
| Cottonseed meal, groundnut meal, groundnut husk | <i>Saccharomyces cerevisiae</i> | Increase in total protein and total aminoacids content; decrease in phosphorus, phytic acid and gossypol content | Not determined | [56] |
| <i>Jatropha curcas</i> seed cake | Isolated bacterial strain (zxy-12) | Increase in aminoacids content and decrease in antinutritional components content (phorbol ester derivatives and curcin) | Not determined | [57] |
| Olive cake | <i>Beauverriabassiana</i> , <i>Fusariumflocciferum</i> , <i>Rhizodiscina</i> cf. <i>lignyota</i> , <i>Aspergillusniger</i> | Increase in protein content and decrease in phenolic, flavonoids and condensed tannins content | Ruminants feed | [58] |
| Stoned olive pomassemed with other wastes (from wheat, barley and crimson) | <i>Pleurotusostreatus</i> , <i>Pleurotuspulmonarius</i> | Significant increase in crude protein and decrease in total phenols content | Not determined | [59] |
| Banana peels | <i>Arxulaadenivorans</i> , <i>Hypocreatocorina</i> | Improvement in hygienic quality; increase in digestibility | Mono-gastric animals feed | [60] |
| Tangerine residues | <i>Lentinus polychrous</i> | Increase in protein content and decrease in phenolic content | Not determined | [61] |
| Pineapple peels | <i>Trichoderma viridae</i> | Increase in total protein content | Feedstock feed | [62] |
| Naptergrass and pangolagrass | <i>Entrophosporasp.</i> , <i>Bacillus subtilis</i> | Increase in protein content; increased in vitro and in vivo digestibility | Chicken feed | [63] |

Biofertilizers

A biofertilizer is a product which contains microorganisms' cells that act in benefit to plant growth by converting an important element to the plant nutrition, e.g., nitrogen and phosphorus, from unavailable to available to the plant. These products, over chemical fertilizers, have the advantage of being environmentally friendly [64]. Phosphorus (P) is the second most demanded mineral nutrient for plant growth, only behind nitrogen (N). Chemical fertilizers containing phosphorus have some shortcomings, such as the large amount of P that is quickly transformed to an unavailable form [65]. Besides, the resources containing the element are being extracted at such high rates that could be depleted in this century. In this regard, phosphate-solubilizing microorganisms (PSM) are a great eco-friendly alternative for the phosphorus nutrition of crops [66].

Aspergillus niger and *Aspergillus fumigatus* were able to solubilize $\text{Ca}_3(\text{PO}_4)_2$, AlPO_4 and FePO_4 at laboratory conditions. The developed biofertilizers were applied to pigeon pea seeds. The *A. niger* product improved growth of the plant [65]. Thermo-tolerant bacteria, actinomycete and fungus were isolated and tested for inorganic phosphate-solubilizing activity [67]. All isolates were able to solubilize $\text{Ca}_3(\text{PO}_4)_2$ and rock phosphate (from Israel). Some isolates could solubilize AlPO_4 , FePO_4 and hydroxyapatite. Agricultural and animal wastes were employed as substrate. The authors emphasized the importance of the thermo-tolerance due to increase in temperature in SSF processes, and consequently the high viability of the product for its application as biofertilizer. Other examples of biofertilizers' production through SSF including microorganisms, substrates and used parameters can be found in Table 5.

Besides PSM, other classic microorganisms are nitrogen fixing and potassium solubilizers. These microorganisms play an important role in enhancing soil fertility, plant growth and, consequently, crop production. Based on that,

a biofertilizer containing N_2 -fixer (*Azotobacter brown* and *Azotobacter chroococcum*), P-solubilizer (*Bacillus megaterium*) and K-solubilizer (*Bacillus mucilaginosus*) was produced using SSF with intermittent air-forced pressure oscillation (PAPO), using steam-exploded wheat straw as substrate. With this system, the bioconversion of wheat straw to biofertilizer was successfully achieved, using the strategy of gas phase control including gas concentration and heat gradient [68]. *Anabaena variabilis* was cultivated on potato waste with an enrichment of N, P and K content of 7.66-, 21.66- and 15-fold when compared to the initial content. The final product offered an economically viable alternative to chemical fertilizers [69].

With the presented information, it is possible to conclude that SSF can be effectively employed to produce biofertilizers, making N, P and K available to plants. As future perspective, studies in economic viability of these biofertilizers using different substrates with comparison to chemical ones are interesting in an economic point of view. Besides, the environmental importance of these products is a great advantage.

Biofungicides

The recurring use of chemical fungicides increases selection pressure and resistance of crop pathogens, which is related to genome mutation [73]. When single-site inhibitors are used, only a single metabolic pathway of the target microorganism is disturbed [74]. On the other hand, multi-site inhibitors target a broad spectrum of pathogens, since they may interfere with thousands of metabolic functions [74] as it acts on multiple sites [73] of metabolism. This mechanism makes it harder for the pathogen to mutate and overcome the multiple effects of a multi-site fungicide. That difficulty is minimized for single-site chemicals because the pathogen needs to change and adapt only one metabolic function to survive. As the single-site fungicides are the modern

Table 5 Production of biofertilizers in SSF by PSMs using different substrates

| PSM | Medium | Parameters | References |
|---|--|------------------------------|------------|
| <i>Bacillus coagulans</i> , <i>Bacillus licheniformis</i> , <i>Bacillus smithii</i> , <i>Streptomyces thermophilus</i> , <i>A. fumigatus</i> | 15% chicken waste, 15% Chinese herbal residue, 35% sawdust, 10% tea residue, 10% paper pulp, and 15% mixture of food proceeding sludge and waste from poultry and livestock slaughter houses | Moisture content 60%; pH 6.9 | [67] |
| <i>Aspergillus fumigatus</i> , <i>Aspergillus niger</i> | 1% cassava starch, 3% poultry droppings, 96% ground cassava peel | Moisture content 50–90%; | [65] |
| <i>Aspergillus awamori</i> | 5 g orange peel, 5% Mussoorie rock phosphate, 4 mL Czapek's mineral salt solution | 75% moisture content, 30 °C | [70] |
| <i>Aspergillus niger</i> | 5 g sugarcane bagasse, 5 g/L Bayóvar rock phosphate | 80% moisture content, 30 °C | [71] |
| <i>Penicillium bilaiae</i> | Thermally treated sewage sludge | – | [72] |

alternatives, since they target desired pathogens specifically [75], they are constantly used to control fungal diseases even when resistance appears. Despite effective, the recurring and inadequate use of those products increase resistance development, affecting crop quality and yield over time.

Although modern chemical fungicides are less harmful than those from older generations, agrochemicals in general still bring damage to the environment, such as environmental, ecological and health problems, severe toxicity, accumulation in food chain and long degradation periods [76]. Therefore, the development of eco-friendly alternatives has been encouraged along the years. Bioproducts with low environmental effects and multiple mechanisms of action have emerged, and they may be plant-derived, such as essential oils like *Thymus vulgaris* oil and *Melaleuca alternifolia* oil that, among others, have presented antifungal activities [76], or they may be antagonistic living organisms [77] as well as their natural metabolites. These bioproducts with antifungal activities are called biofungicides, and they can be produced in a variety of ways.

Biofungicides produced by SSF consist mainly of fungi or bacteria, the biocontrol agents, capable of controlling fungal diseases. Choosing the right antagonistic microorganism is important to develop an effective product as it needs to target the desired pathogen and control it, by neutralizing it or limiting its growth. The ability to control other organisms is mainly due to multiple antagonistic mechanisms such as competition for nutrients, secretion of lytic enzymes, direct parasitism and secretion of toxic metabolites [78]. This multiple approach decreases the chance of resistance by pathogens, which is one of the reasons why integrated disease management is interesting for effective disease control and maintaining high yields [79]. *Trichoderma*, for example, is one of the most studied biocontrol agents and has

been proved to be efficient against several plant pathogens such as: *Phytophthora*, *Rhizoctonia*, *Sclerotium*, *Pythium*, *Fusarium*, *Sclerotinia*, *Gaeumannomyces* [78], *Botrytis* [80], *Rhizopus*, *Alternaria*, *Macrophomina*, *Colletotrichum*, *Ganoderma* [79] and several others.

Solid-state fermentation exerts a positive effect on biofungicide development considering that the mostly used solid organic wastes resemble the microorganisms' natural habitat and help them thrive [81, 82]. However, besides being able to grow on domestic and agro-industrial wastes, an inert solid material impregnated with a proper liquid medium can also be used as a substrate for colonization and spore production [83, 84]. Cassava wastewater, for example, was mixed to kaolin powder, a clay mineral, by Alex et al. [85] to obtain grains, after proper drying, and serve as solid substrate for *Trichoderma virens* spore production.

Wheat bran, rice husk, pea seed cover, sorghum grain, rice straw, tea leaf waste, coffee husk, oil cakes, sugarcane bagasse, molasses, sawdust, orange peel, maize spent cob, vegetable waste, corn flour, palm leaves, date seeds and farmyard manure [78, 79, 83] are just some examples of substrates that can be used for mass production of conidia or cells as biofungicides. Although antagonists themselves make a great part of biofungicidal products, they also produce secondary metabolites that may serve as biocontrol substances. Those metabolites can also be obtained via SSF, recovered and used on the field. The production of those substances, however, is influenced by different stimuli [85] or presence of specific inducers in the culture medium. Gliovirin, a substance that inhibits growth of species of *Phytophthora*, for example, needs amino acids as a nitrogen source [85] to be produced. Therefore, a substrate with low levels of these specific molecules will probably result in low yields of gliovirin production. Biosurfactants, antifungal proteins

Table 6 Biofungicides produced in SSF using different biocontrol agents and substrates

| Biocontrol agent | Substrate | Production | Time | Target | References |
|-----------------------------------|---|--|---------|--|------------|
| <i>Trichoderma virens</i> | Kaolin supplemented with Cassava wastewater | 1.13×10^6 spores g^{-1} kaolin | 10 days | <i>Phytophthora palmivora</i> | [85] |
| <i>Streptomyces similanensis</i> | Rice bran + coconut husk | 2.1×10^9 CFU g^{-1} dried solid | 7 days | <i>Phytophthora palmivora</i> | [86] |
| <i>Streptomyces hygroscopicus</i> | Wheat bran + vermicompost | 5.3×10^{10} CFU g^{-1} | 7 days | <i>Verticillium dahliae</i> ; <i>Fusarium oxysporum</i> | [87] |
| <i>Penicillium frequentans</i> | Peat + vermiculite + lentil meal | 4.5×10^8 conidia g^{-1} dry substrate | 5 days | Monilinalaxa | [88] |
| <i>Coniothyrium minitans</i> | Oat grains | 6×10^{14} conidia m^{-3} | 13 days | <i>Sclerotinia sclerotiorum</i> | [89] |
| <i>Dicymapulvinata</i> | Parboiled rice | 7.77×10^6 spores g^{-1} substrate | 17 days | <i>Microcyclusulei</i> | [90] |
| <i>Paecilomycesvariotii</i> | Jatropha oil cake | 6.7×10^9 spores g^{-1} substrate | 10 days | <i>Fusarium oxysporum</i> ; <i>Verticillium dahlia</i> | [34] |
| Rhamnolipid biosurfactant | Mahua oil cake | – | 7 days | <i>Fusarium oxysporum</i> f. sp. melongenae | [91] |
| β -glucosidase | Apple pomace | 91.8 ± 7.12 IU.gfs $^{-1}$ | 2 days | – | [92] |

and hydrolytic enzymes are some other examples of metabolites that work as pathogen inhibitors, as long as they have antifungal activity. Table 6 shows some examples of biofungicides produced using SSF.

Solid-state fermentation is carried out with one or more solid substrates, in the absence of free water [81], but with adequate moisture. The basic concept of production is substrate colonization in order to produce conidia [84]. The substrate must have an adequate size of particle, and proper aeration between them must be ensured. Optimal temperature will vary among species, as some fungi grow in lower or higher temperatures, such as *Trichoderma koningii* that can grow at 40 °C [79]. Most commercial formulations are emulsifiable suspensions or wettable powder [84]. So, after colonization, spores may be recovered or the colonized substrate may be ground to powder [78] before complementing the formulation with additives, like carriers and adjuvants, to ensure proper suspension and extended shelf-life. Common application methods include seed treatment, soil application and aerial spray for foliar application. The ideal choice will depend on the relationship between target microorganism and the antagonist.

Spores' production (*Trichoderma*, *Metarhizium*, *Beauveria*)

Biofungicides are generally administered as fungal spores [93], and solid-state fermentation is the most popular method to mass produce *Trichoderma*, as well as for *Metarhizium* and *Beauveria*, since most bioproducts based on entomopathogenic fungi also have infective aerial conidia as active agents [94]. SSF does have some disadvantages when compared to submerged fermentation, such as increase in metabolic heat, difficulty in measuring and controlling parameters like pH and water content, and possible need to pre-treat substrates [93]. However, SSF also has several advantages. It provides better yield, low risk of contamination, toleration of downstream processing, cost-effectiveness [79], especially when agro-industrial wastes are used as substrates, minimization of effluents, since there is no liquid phase, easy aeration and unnecessary agitation [93]. For spore production, SSF is probably the best method because fungi usually generate vegetative propagules in submerged fermentation conditions. Those structures are less tolerant to adversities than conidia [94], so it may not resist to drying processes and storage, for example.

Besides production yield, the final characteristics of conidia are directly affected by growth conditions, biotic and abiotic factors. Parameters like pH, temperature, water activity, humidity, aeration, light and medium composition [94] directly influence growth and production. For some species, such as *T. atroviride*, *T. humatum* and *T. pleuroticola*, temperature is a limiting factor in production and biological

activity. Most *Trichoderma* species grow in the range of 25–30 °C [79]. Incubation temperature for *Beauveria* and *Metarhizium* usually also varies between 25 and 30 °C [95–98]. For the three of them, initial moisture content may vary from 40 to 70%, depending on the substrate used and its capacity to absorb water, and typical production cycles vary between 7 and 15 days [78, 84, 94–97]; however, some processes may take more time. As mentioned before, plenty of substrates may be used for fermentation via SSF. Fungi like *Trichoderma*, which are able to take up nutrients from lignocellulosic materials, have more options of substrates to thrive. Yet, there are plenty of alternative agro-industrial wastes and by-products to be explored by those that do not have the same ability.

After the substrate is colonized, the conidia must be harvested. They can be washed from the substrate using surfactants or extracted by sieve extraction and vacuuming. However, a simpler option is to air dry the colonized substrate and then grind it to powder [78, 99]. The drying process is critical for shelf-life so it is important to have a low moisture content of at most 7% [84] to provide more stability. Maintaining the viability and stability during storage is a great concern of bioproduct manufacturers [84]. Furthermore, it is important to guarantee extended shelf-life on ambient temperatures to lower costs and energy requirements.

All the additives necessary to ensure proper suspension, delivery of the active agents and performance on field are included to the formula after the drying process. Wetting agents, suspension agents, dispersants, antifoamers, emulsifiers and spreaders may be incorporated to the formula. At least, a wetting agent must be added for proper suspension of hydrophobic aerial conidia [84]. As biocontrol agents can be delivered to crops in different ways, such as aerial spraying, soil treatment, root treatment and seed treatment [78], a different formulation may be needed for each goal because each of them requires different levels of adherence to different parts of the plant. Additives are also responsible for maintaining residual activity of bioproducts, as they may lose viability due to environmental exposures, such as UV light and excessive or insufficient moisture [100]. To be considered an effective and efficient bioproduct, it must have proved antagonistic activity, which is measured by the amount of the biological control agent required to initiate infection and neutralize the pest, and in terms of efficiency, biocontrol is measured by pest mortality.

Bioinsecticides

While biofungicides are biological agents that control fungal diseases, bioinsecticides control insects. Just as the first, substances obtained from living organisms, like plants, animals, bacteria, nematodes or even other insects [100, 101], can be

considered bioinsecticides. Additionally, genetically modified plants, minerals and viruses can also be categorized as such bioproducts. Entomopathogenic bacteria or fungi are microorganisms able to parasitize insects and neutralize or disable them. Many of them can be easily produced by SSF, like the fungi *Beauveria* and *Metarhizium*.

Beauveria and *Metarhizium* bioproducts represent 70% of the global market of mycopesticides [102]. The most known species are *B. bassiana*, *B. brongniartii* and *M. anisopliae*. However, *Isaria fumosorosea*, *I. javanica*, *I. clade* [101], *Lecanicillium lecanii*, *Nomuraearileyi* and *Hirsutellathompsonii* [103] are some other species of fungi also known to control insect pests. These fungi are constantly used to control foliar pests, such as beetles [101], white flies, aphids, thrips, mites, leafminers, plant bugs and soil pests [103]. When these fungi act as insect parasites, they start growing internally in the host, producing toxins and draining the nutrients from the insect [104]. After neutralizing their prey, some species, like *B. bassiana*, discharge millions of new infectious spores on the surface of the host.

Those fungi can grow on solid substrates and are usually produced on cooked cereal grains, like rice and millet [99]. As rice grains may increase the costs of the final product, Silva et al. [102] managed to produce 8.1×10^9 conidia g^{-1} dry substrate of *B. bassiana* and 3.3×10^9 conidia g^{-1} dry substrate of *I. javanica*, after 144 h, using palm kernel cake, showing its potential to produce biocontrol agents. Other by-products or agricultural wastes, like brewer's spent grains [105], bagasse, tapioca rind and coconut cake, can also be used. However, lignocellulosic materials are not very well consumed by some species due to its complex composition and the inability to produce specific lignocellulose-degrading enzymes [102]. Therefore, such types of material may only serve as a supporting matrix for growth.

Although those are well-known entomopathogenic fungi, the most successful bioinsecticide is *Bacillus thuringiensis* [106]. It gained popularity for being used to control caterpillars [101], dominating the microbial pesticide market afterwards. Various strains of these spore-forming bacilli produce highly selective insecticidal toxins [107], called Cry or Cyt toxins, which are water soluble proteins that present as crystal inclusions upon sporulation. *B. thuringiensis* control insect pests on their larval stages, disrupting their midgut tissue [106]. Most bioproducts made with this biological agent are spore-crystal preparations. Some well-known subspecies that produce slightly different proteins are *B. thuringiensis* var *kurstaki*, *B. thuringiensis* var *aizawai*, *B. thuringiensis* var *san diego* and *B. thuringiensis* var *tenebrionis*. Although most of *B. thuringiensis* products are effective against plenty of leaf-feeding lepidopterans, each of those strains is more suitable for a particular insect pest.

Some non-spore-forming bacteria can also be effective biocontrol agents. *Serratia entomophila*, pathogen of the

New Zealand grass grub *Costelytrazealandica*, and *Chromobacterium subsugae*, parasite of a range of insects, are some examples of that. Other bacteria with great insecticidal activities, like *Yersinia entomophaga* and *Pseudomonas entomophaga*, however, have yet to be developed as bioproducts [107].

Bacteria-based bioinsecticides produced via SSF grow as biofilms, and just like fungi, low cost materials, such as husks and brans [107], soybean seeds, lime powder [108] and broiler litter [109], can also be used for mass production. On broiler litter, for example, it is possible to obtain $1\text{--}5 \times 10^9$ spores g^{-1} litter after 40 h [109]. In 36 h of SSF, using wheat bran and perlite, 8.2×10^9 spores g^{-1} and 820 IU mg^{-1} dry wt can be recovered [107]. Choosing the right substrate to fit the microorganism's needs is an important part of the process, since it can provide better outcomes.

Other biopesticides

Biopesticides are defined as biological agents or bioactive compounds produced from bacteria, fungi and protozoa, which are applied to suppress pests that attack crops, such as fungi, insects, weeds, nematodes or other pests [110]. Bioherbicides are responsible for eliminating weeds and other plants. They were first used in 1973, when the ability of *Phytophthora palmivora* was discovered to eliminate strangler vine [111]. These products have great difficulty entering the market when compared to chemical herbicides, especially in terms of their effectiveness [112]. However, much research is being done to increase its performance and overcome the restrictions of applying a biological agent against plants on the field [113].

In general, bioherbicides are produced by organisms that are naturally phytopathogens, transforming a plant's disease into a product that benefits other plants [114]. Some involved species of fungi can be cited such as *Chondrostereum purpureum* [115], *Colletotrichum gloeosporioides* [116], *Sclerotinia minor* [114], *Phomamacrostroma* [111], some bacteria such as *Xanthomonas campestris* [117] and plant extracts as *Parthenium hysterophorus* [118].

Several substrates can be employed in the development of bioherbicides through SSF with good effectiveness. The most employed are agricultural residues involving sugarcane bagasse, wheat bran, rice straw, corn, soybean and different pomaces [93, 113]. Watson [114] obtained a bioherbicide named Sarritor, based on the fungus *S. minor* IMI 344141 using ground barley in SSF, after 7 days between 15 and 24 °C. Bailey and Falk [111] developed another product composed by *P. macrostroma* 94-44B grown on different types of grain using SSF.

Another type of biopesticide is the bionematicide, responsible for eliminating plant nematodes. Unlike bioherbicides, bionematicides are easier to enter the market [119]. They

are able to parasitize and prevent nematode eggs, young and adult individuals [120]. In addition, the environmental impact caused by them is lower than chemical nematicides, causing no toxicity to plants or releasing harmful gases [121]

Similar to bioherbicides, bionematicides start from natural pathogens to worms, such as the fungi *Myrothecium verrucaria* [119], *Paecilomyces lilacinus* [120], *Pochoniachlamydo sporia* [122], the bacteria *Pasteuriapenetrans* [123], *Bacillus firmus* [121] and plant extracts (*Carum carvi*) [124]. Several studies target these species against Root-knot nematodes, especially *Meloidogyne javanica*, a nematode that attacks cereal, fruit and flower crops and can cause loss of up to 100% of plants [124, 125].

Many of these products are originated from culture media for the biological agent growth, again highlighting SSF and the use of agro-industrial residues in the cultivation of fungi [93]. Brand et al. [126] produced a bionematicide based on the *P. lilacinus* in order to control *Meloidogyne incognita*, obtaining 10^9 spores per g of dry substrate. Coffee husks, defatted soybean cake, cassava bagasse and sugarcane bagasse were used in SSF, for 10 days at 28 °C. Mousumi et al. [127] optimized a culture medium composed of wheat bran, beer waste, sugarcane bagasse, coffee husk and spent tea waste for *P. lilacinus* KU8 cultivation. After 24 h at 30 °C in SSF, 107.46 mg of biomass g^{-1} was reached, with activity against *Meloidogyne*.

Plant growth hormones

Phytohormones are typically found in plant tissues and low concentrations of these molecules can promote several advantages to plant growth, such as enlargement and differentiation, organ senescence and abscission, and cell division. Several phytohormones were discovered such as auxins, cytokinins, abscisic acid, gibberellins and ethylene [128].

Gibberellic acid (GA_3) is a plant growth hormone that can be found only in low amounts in plants, what encouraged its production by fermentation, where SSF is certainly a good alternative. This phytohormone belongs to the gibberellins family and acts in benefit of seed germination, responses to abiotic stress, fruit growth enhancement, stem elongation, flowering, the malting of barley, and when in interaction with other phytohormones can promote different beneficial physiological effects [129].

Different substrates have been used for GA_3 production in SSF, such as citric pulp [130–132], pigeon pea pod, pea pod, corn cub, sorghum straw [133], coffee husks [134], wheat bran [135–137] and others (Table 6). Media supplementation with carbon sources can be carried out using sucrose and starch. Nitrogen sources must also be added to the medium for regulatory reasons. However, GA_3 synthesis starts with exhaustion of nitrogen. Based on that, better yields of GA_3 production are usually achieved with C/N ratio of 6:1 to

45:1. Different microorganisms, such as fungi and bacteria, can produce this hormone, being *Fusarium fujikuroi* and *Fusarium moniliforme* the most commonly used [129]. More information about microorganisms, media, parameters and yields of GA_3 production can be found in Table 7.

Auxins are positively involved in several plant processes, such as elongation, fruit and embryo development, vascular tissue differentiation, organogenesis, root patterning, tropistic growth, apical dominance and apical hook formation [142]. Prado et al. [143] worked in the production of indole-3-acetic acid (IAA) through SSF, a type of auxin, which was identified by LC–MS/MS. The authors achieved best results utilizing *Bacillus subtilis* cultivated in wheat bran, *Trichoderma atroviride* in soybean bran, and *A. niger* in wheat bran. An improvement of tenfold IAA production was achieved with the presence of tryptophan (1%, w/w). Higher IAA productions were reached by *B. subtilis* and *T. Atroviride* with the use of low lignin content substrates, and substrates with high hemicellulose concentrations and neutral pH for *B. subtilis*.

Abscisic acid (ABA) is another plant hormone that plays an important role in plant growth regulation, assisting in the increase in crop yields [144]. Although ABA has been reported as a product of some microorganisms, such as the phytopathogens *Mycosphaerella rosicola* [145], *Botrytis cinerea*, *F. oxysporum* and *Rhizoctonia solani* [146], the number of reports about the use of SSF on its production is not significant. Marumo et al. [147] reported the synthesis of ABA in a process using dextrose agar medium inoculated with *B. cinerea* and incubated for 7 days at 27 °C. No more data on the production of ABA by SSF were found.

There are reports on the production of cytokinins by phylloplane bacteria [148] and ethylene by *Pseudomonas*, *Xanthomonas* and *Erwinia* [149]. However, little scientific production using SSF was found. In relation to ethylene, Tao et al. [150] produced the hormone in SSF using wheat straw and bran as substrates by a transformed strain of *Trichoderma viride*, which contained a gene encoding an ethylene-forming enzyme from *Pseudomonas syringae* pv. *glycinea*. The production reached 2280 nL of ethylene. According to the authors, this efficient production is attractive to industrial use. Unfortunately, no scientific data were found on the production of cytokinins using SSF.

Probiotics (*Bacillus*)

The word *probiotic* derives from the Greek *in favor of life* and was used for the first time by Lilly and Stillwell in 1965, undergoing several modifications in its definition [151]. Currently, probiotics are defined as living microorganisms that, when administered in adequate amounts, confer benefits to the health of the host [152]. Probiotic products have been

Table 7 Production of GA_3 using different substrates in SSF

| Microorganism | Medium | Parameters | Production | References |
|------------------------------|--|--|--|----------------------------|
| <i>F. fujikuroi</i> | 100 g wheat bran; 20 g soluble starch; 3 mL linseed oil; 0.15 g urea; 60 mL mineral salt-acid solution | 28 ± 1 °C; fed-batch culture | 1.3 g/kg | Kumar and Lonsane [136] |
| <i>F. fujikuroi</i> | 100 g wheat bran; 20 g soluble starch; 1 g linseed oil; 70 mg urea; 7 mg $MgSO_4 \cdot 7H_2O$ | 50% moisture content | 1.116 g/kg | Kumar and Lonsane [135] |
| <i>F. fujikuroi</i> | 6 g wheat bran-starch based medium: 10 mL nutrient solution (240 g/L maltodextrins, 4.0 g/L ammonium tartrate, 12 g/L potassium phosphate, 1.2 g/L magnesium sulfate and 0.2 g/L yeast extract) | 55% moisture content; 28 °C; airflow rate 4 L/g/h; packing density 0.3 g/cm ³ | 6.8 g/kg | Agosin et al. [137] |
| <i>F. fujikuroi</i> | 1 kg wheat bran; 250 g soluble starch | 50% moisture content; 28 °C; airflow rate 15 L/min/kg; fed-batch pilot-scale reactor | 3 g/kg | Bandelier et al. [138] |
| <i>F. fujikuroi</i> | 20 g cassava; 12 g bagasse; 4.4 g low density polyurethane | 60% moisture content; 29 °C; airflow rate 0.21/h/g | 0.25 g/kg | Tomasini and Fajardo [139] |
| <i>F. fujikuroi</i> | Coffee husk pre-treated with KOH (g/L) | 60% moisture content; 29 °C | 0.99 g/kg | Machado et al. [134] |
| <i>F. moniliforme</i> | Citric pulp impregnated with nutritive solution containing $FeSO_4 \cdot 7H_2O$ and $(NH_4)_2SO_4$ | 75–80% moisture content; 29 °C | 5.9 g/kg | Rodrigues et al. [131] |
| <i>Fusarium proliferatum</i> | 25 g of pigeonpeapod, corncobs, sorghum straw or pea pod; 20 mL nutrient sucrose medium (sucrose 80 g/L; $MgSO_4 \cdot 7H_2O$ 1 g/L; KH_2PO_4 5 g/L; NH_4NO_3 0.48 g/L; $ZnSO_4 \cdot 7H_2O$ 0.0032 g/L; $CuSO_4 \cdot 7H_2O$ 0.0003 g/L; $Na_2MoO_4 \cdot 7H_2O$ 0.0002 g/L; $MnSO_4$ 0.0002 g/L) | 70% moisture content; 29 °C | Using: pigeon pea pod: 78 g/kg; pea pod: 64 g/kg; corncobs: 61 g/kg; sorghum straw 55 g/kg | Satpute et al. [133] |
| <i>F. moniliforme</i> | 5 g jatropha seed cake; 8 mL mineral salt solution ($CuSO_4$ 0.007 g; $FeCl_3$ 0.007 g; $ZnSO_4$ 0.007 g dissolved in 1 L of 0.2 mol/L HCl) | 60% moisture content; 30° | 1.050 g/kg | Rangaswamy [140] |
| <i>F. moniliforme</i> | Citric pulp supplemented with sucrose | 70% moisture content | – | Silva et al. [132] |
| <i>F. moniliforme</i> | Citric pulp impregnated with nutritive solution containing 1.5 g/L urea and 1.5 g/L $MgSO_4 \cdot 7H_2O$ | 75% moisture content; 29 °C | 7.34 g/kg | Oliveira et al. [130] |
| <i>Fusarium oxysporum</i> | 10 g sesame bark, wheat straw or date waste; 3 g sucrose; 0.3 g $NaNO_3$; 0.1 g K_2HPO_4 ; 0.05 g $MgSO_4 \cdot 7H_2O$; 0.05 g KCl; 0.001 g $FeSO_4$ | 70% moisture content; 30 °C | 8.16 g/kg | Rhouma et al. [141] |

used since the most remote times of humanity, especially in products derived from milk and seeds [153].

The first step in the production of a probiotic involves selecting a microorganism with beneficial features, such as strengthening the intestinal microbiota and acting against pathogens [154]. Among the microorganisms that are used, the vast majority are formed by bacteria, in general lactic acid bacteria, such as *Lactobacillus*, *Lactococcus* and *Enterococcus*, in addition to bacteria such as *Bifidobacterium*, yeasts and other fungi [155, 156]. However, the *Bacillus* genus has been gaining space in the probiotics market, especially due to its spore formation capacity and, therefore, the formation of a product resistant to adverse conditions [157, 158]. *Bacillus* strains with a probiotic character mainly include the *B. subtilis*, *B. licheniformis* and *B. amyloliquefaciens* species [159–161], and also some species such as *B. coagulans* [162] and *B. indicus* [163].

The second step is to establish the medium in which the microorganism will grow. In the food industry, the main media are formed based on milk or its derivatives, serving lactic acid bacteria and allowing them to maintain the same sugars in fermentation and in the final product [151, 155]. However, alternative media are increasingly frequent, employing agro-industrial residues and using SSF conditions [164]. By-products of agriculture of soy, corn, rice and carob are the most common for cultivation of *Bacillus*, having their origin in traditional naturally fermented foods [158]. The fermentation conditions in the solid state also favor sporulation, given the low humidity rates and susceptibility to pH changes [165].

Terlabie et al. [166], for example, achieved a *B. subtilis* cell count between 10^{10} and 10^{11} CFU g⁻¹ in 24 h using soybeans in SSF. They started from a naturally fermented African food, dawadawa and inoculated the microorganism in freshly sterilized grains, kept at 30 °C. Another example was developed by Zhang et al. [167], who co-cultivated *B. subtilis* and *Lactobacillus reuteri* using soybean meal, corn flour and wheat bran. After an optimization, it was possible to obtain between 10^9 and 10^{10} CFU g⁻¹ for each microorganism in SSF, after 48 h at 37 °C. Berikashvili et al. [168] cultivated *B. amyloliquefaciens* also in SSF, with media containing wheat bran, ethanol production residue, sunflower oil mill, corncobs, soybeans and other agro-industrial wastes. By using corncobs enriched with cheese whey, they obtained 10^{11} spores g biomass⁻¹, after cultivation at 37 °C for 4 days, demonstrating another example with high spore productivity.

In addition, in recent decades, probiotics began to be administered in animal feed as an alternative to antibiotics, in order to prevent the transmission of bacterial resistance to human pathogens [169, 170]. The benefits generated by the ingestion of these microorganisms include improved nutrient digestibility, modulation of intestinal microflora, increased feed conversion rate, inhibition of pathogens and reduced

nitrogen in feces [171–173]. The application of probiotics is being tested and the benefits proven in broiler birds [174], piglets [175], ewes [176], fishes [159] and crayfishes [177], demonstrating their immense potential for livestock.

Solid-state fermentation advancements and innovation

Although the idea and practice of SSF are ancient, its evolution was remarkable in the last 50 years. A patent and scholarly work search was done using the database Lens (www.lens.org) and analyzed using MS Excel®. Until 1970, relatively few patents and scholarly works were done in the field, mostly dealing with specialty chemicals and nucleotides. Presumably, basic processes such as koji fermentation were not patentable (although specific improvements of the technology were). From 1975 on, the number of patents jumped from a dozen per year to thousands—reaching ca. 40,000 patents in this last decade. Research, in the meantime, also grew exponentially, at 360% per decade, on average. The evolution of patents and research articles on SSF in the last 90 years is shown in Fig. 3.

The analysis of the patent set for SSF (76,532 patent families) shows the evolution of the technology from specialty antibiotics, metabolites and composting pre-1970 to enzymes, antibiotics and feed enzymes dominating the landscape from 1970 to 2000. The new century saw the appearance of genetically modified organisms, the resurgence of SSF associated with grain ethanol production, and since 2010 the production of cellulosic ethanol and keto-gluconic acid. Enzymes and antibiotics never lost the importance throughout time, but various specialty metabolites grew importantly after 1990. The top players in the field are Novozymes, Du Pont, DSM, Monsanto, Genentech, Nestec, Xyleco and MS Technologies—all companies linked to agro-industrial crops, feed, food and bioenergy production.

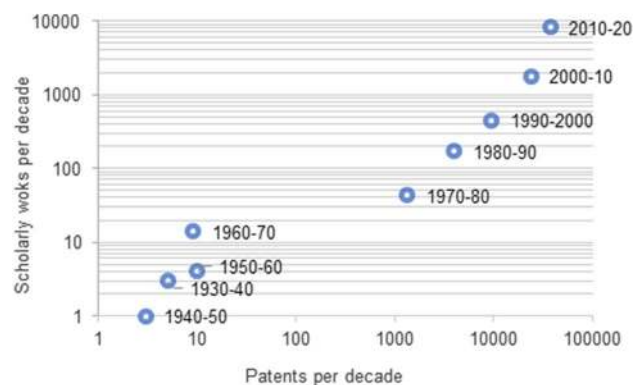


Fig. 3 Evolution of publications and patents in solid-state fermentation

The scope of papers in SSF has been directed towards three axes: technological improvements and engineering aspects, agroindustry residues usage and specific metabolites. The research interest shifted from Japan, Bangladesh, EUA, Egypt and UK pre-1970s, to EUA, China, India, Brazil and Spain in the last decade—not that the research lost importance in other countries. However, SSF picked up steam in developing countries, possibly because of the availability of cheap, high-quality substrates and the need to valorize them through bioprocesses.

In order to assess the status of scientific and technological advancements and innovation in the area of SSF applied to agriculture and related products, two document searches were performed, one for scientific research papers and the other for patent documents. Although patent documents are not a direct measure of innovation, it was assumed that they represent technological development, which can potentially result in innovation if disseminated to society.

Research articles were searched in the Science Direct database (www.sciencedirect.com) containing the words (solid AND state AND fermentation) in the title, abstract or keywords and the words (agriculture OR agricultural OR crop OR agroindustry OR agro-industrial OR horticulture OR agronomy OR agronomic) in the whole document, in the period of 2010 to 2020, with the aim to retrieve documents on SSF processes related to agriculture and agricultural products. The patent search was performed in the Derwent Innovations Index database using the following keywords in the topic (TS=solid AND state AND fermentation) and applying the filter “agriculture” in the field of knowledge, also in the period of 2010–2020. A manual selection was performed in the data exported to MS Excel® to exclude documents that were not the object of interest of this study, based on the analysis of the title and abstract.

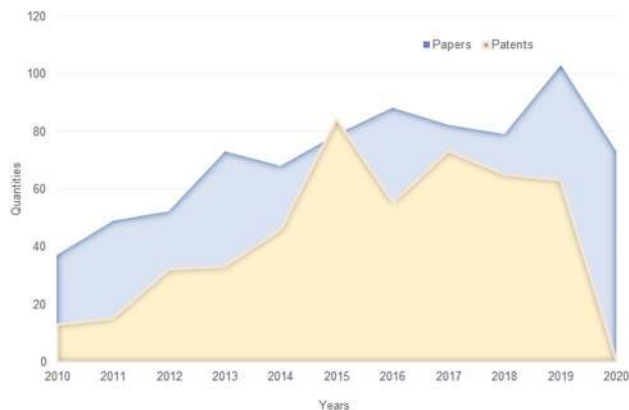


Fig. 4 Number of scientific research papers and patent documents published in the last decade. Date of search: April 22nd, 2020. Sources: www.sciencedirect.com and Derwent Innovations Index (Web of Science)

There was a tendency of a linear increase in the number of publications over time, both for scientific research papers and patent documents (Fig. 4), considering that the year 2020 is not yet completed, and that there is a latency period of usually 18 months between the filing and the publication of a patent document [178]. This demonstrates that the interest in this theme is increasing and that scientific and technological developments are still needed. A total of 783 scientific publications and 479 patent documents were retrieved. The number of scientific papers is greater than the number of patent documents except in the year of 2015, when a peak was observed for the published patent documents (84), surpassing the number of research papers. Considering the latency period, these documents were filed between 2013 and 2014. However, it was identified that, from this amount, 19 documents were filed by a single institution, the Chinese Jiangnan University. In this sense, this peak represents an isolated event that changed the curve tendency.

The main patent filing countries were China, South Korea, India and the USA. Other countries, such as Brazil, France, Indonesia, Malaysia and Mexico, also appeared in the technological map. However, the technology holder is China with 89% of patent documents.

Among the patented biproducts are, for example, different types of biofertilizers (CN110713394-A) [179] containing microorganisms such as the bacteria *Pseudomonas*, *Azotobacter*, *Bacillus* and *Rhizobium* [180, 181] participate in the nutrient absorption process (N, P, Cu, Fe) and in the ecological balance of the soil, which is reflected in plant immunity, health and growth (WO2019217548-A1) [182]. In the case of the fungus *Trichoderma*, for example, some strains have the ability to eliminate the phytopathogen *Fusarium oxysporum* [183].

Patent documents related to food or animal feed with probiotics (CN110384176-A) [184], and *Hermetiailucens* proteins, which increase the effectiveness of the nutrients contained in the food, its absorption in the intestinal tract, in addition to modulating the intestinal flora and promoting both growth and productivity (CN110037165-A) [185], were also retrieved. Fermented products of *Lactobacillus bulgaricus* and *Streptococcus thermophilus* employed to reduce postpartum syndrome especially in pigs (CN110037189-A) [186] and production processes for some vitamins, oligosaccharides, enzymes and organic acids for animal feed were also claimed in the patent documents.

Utility models of bioreactors were identified in many patent documents. For example, the CN206476905-U document described the design of a horizontal tank bioreactor for the treatment of organic solid waste equipped with a mechanical screw-type agitation system. The design guarantees high efficiency in the fermentation tank, as well as high equipment life [187]. Deng and Liang [188] claimed an automatic tray fermenter for SSF, in which the trays are automatically

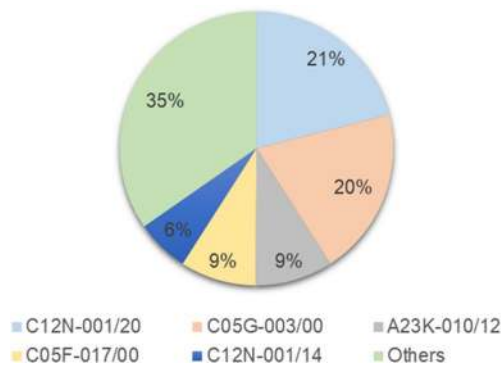


Fig. 5 Distribution of patent documents according to WIPO's International Patent Classification codes (IPC) Legend of IPC codes: C12N 1/20: Bacteria; Culture media therefor; C05G 3/00: Mixtures of one or more fertilizers with additives not having a specifically fertilizing activity; A23K-010/12: Foods or foodstuffs; their treatment, not covered by other classes by fermentation of natural products, e.g., of vegetable material, animal waste material or biomass; C05F-017/00: Preparation of biofertilizers characterized by biological or biochemical treatment steps, e.g., composting or fermentation; C12N 1/14: Fungi (culture of mushrooms A01G 18/00; as new plants A01H 15/00); Culture media therefor

unloaded, which increases efficiency, significantly decreases operating time, as well as the amount of waste generated (CN105837278). Mai and Mai [189] described a utility model in which a bioreactor with a rotating box, based on a Turnover Box, was designed. The equipment comprises a fermentation cabin connected with a quantitative compartment and a loading and unloading structure in the fermentation unit. One of the problems that the utility model solves is the technical deficiency with respect to the use of space, in addition to the versatility of the equipment, since it can be used in different types of fermentations.

The top-two most recurrent International Patent Classification (IPC) codes [190] among the retrieved patent documents were C12N 1/20 (Bacteria; Culture media therefor), in 21% of the documents, and C05G 3/00 (mixtures of one or more biofertilizers with additives not having a specifically fertilizing activity), in 20% of the documents. The five most recurrent classification codes, comprising approximately 65% of the documents, are presented in Fig. 5.

The results of the scientific papers and patent documents search indicated that the SSF technology in the area of agriculture and agricultural bioproducts is not a mature technology yet, and both scientific and technological developments are required to promote diffusion and consequently innovation. There are still technical obstacles to be overcome, such as homogenization problems and difficulties in scale-up, so that the SSF technology can transcend the traditional applications of composting and silage. But there are good perspectives since growing technological development was

identified, based on invention patent and utility model documents, for products, processes and equipment.

Conclusions

Solid-state fermentation (SSF) is characterized by the reuse of agro-industrial and/or alternative sub-products as substrate/support for bioproducts production including some traditional processes such as fermented food in the Eastern countries. The potentialities of SSF technique must be evaluated for each process. Animal feed and agricultural bioproducts can be efficiently produced through this simple technology that continues to raise attention of scientists and industries around the world. Factors that limit the scale-up of laboratory-scale SSF developed processes are still observed. The choice of the correct microorganisms, substrate/support and bioreactor is predominant, affecting the economic viability of the SSF process, which depends on a careful comparison with submerged fermentation processes. Good perspectives for SSF applied to agriculture and animal feed can be observed since there was a linear increase in the number of publications over time, which is still growing, both for scientific research papers and deposited patent documents. This demonstrates that the interest in this theme is increasing and that scientific and technological developments are still needed.

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Author contributions LPSV was involved in conceptualization, literature research, bioreactors, abstract–conclusions, final revision. AP contributed to structure/final revision. JCC helped in introduction, patents and innovation. LAJL and ALW were involved in SSF substrates characterization and application. SGK and WJM contributed to patents and innovation. ROP helped in biofertilizers and plant growth hormones. LWH was involved in biopesticides, probiotics and other bioproducts. AOR contributed to biofungicides, bioinsecticides and spores. VTS was involved in animal feed products. CRS and corresponding author helped in structure and final revision

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All authors agree with their participation in this paper

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