Exploration of Foods and Foodomics

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Solid-state fermentation: an alternative for continuous and discontinuous production of bioactive compounds with biological activity

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Academic Editor: Jose Mendiola, Institute of Food Science Research (CIAL-CSIC), Spain

Received: January 25, 2025 **Accepted:** May 15, 2025 **Published:** June 16, 2025

Cite this article: De La Rosa-Esteban K, Sepúlveda L, Buenrostro-Figueroa JJ, Chávez-González ML, Estrada-Gil LE, Saenz-Galindo A, et al. Solid-state fermentation: an alternative for continuous and discontinuous production of bioactive compounds with biological activity. Explor Foods Foodomics. 2025;3:101085. https://doi.org/10.37349/eff.2025.101085

Abstract

Bioactive compounds are secondary metabolites widely studied for their benefits to human health. They are distributed in various fruit, vegetable, and plant peels. The application of sustainable techniques for the extraction of these compounds is being implemented, assisted extraction by solid-state fermentation is a sustainable and effective alternative for the recovery of bioactive compounds by using agro-industrial waste as a raw material for extraction, this being a green process, easy for implementation, and it has low water and energy consumption. This research presents the biological properties of some of the most used bioactive compounds in the industry, as well as the advantages and factors that influence solid-state fermentation and the different processes for their recovery and/or production. The production of bioactive compounds using both continuous and discontinuous processes come with unique advantages and challenges. The choices between these methods depend on specific production objectives, scalability needs, and the availability of resources. As a result, ongoing advancements are refining these methods, enabling more sustainable and efficient production of bioactive compounds.

Keywords

Production, bioprocess, agro-industrial wastes, biological activity

Introduction

Plants often possess biological compounds known to be secondary metabolites that the plant produces naturally. Recent studies have considered some primary metabolites as bioactive compounds. Bioactive compounds play an important role in human health and they can be easily found in some fruits, vegetables, legumes, cereals, and roots [1–3].

Bioactive compounds can be divided into essential compounds and non-essential compounds. Essential compounds play a biological function in the human body and often a deficiency of these can lead to disease, examples of these compounds are liposoluble vitamins. On the other hand, non-essential compounds are as their name suggests not essential to the human body but that doesn't mean they are not important, phytochemicals are an example of this and they can offer several health benefits such as the prevention of disease, and another important function is the antioxidant power which can lead to other important functions [4].

Phytochemicals are one of the most important varieties of bioactive compounds and they come from plants. The consumption of phytochemicals could potentially protect the body from diseases. In recent years, phytochemicals have generated great interest in their various applications, one of them being the development and application of phytochemicals in nutraceuticals and food supplements. Phytochemicals can be found in almost all the foods from vegetable sources [5, 6]. These compounds have high antioxidant, antiviral, antimicrobial, anthelmintic, and antiallergenic activity [7].

According to the chemical structure presented, bioactive compounds can be classified as: polyphenols, alkaloids, phytosterols, terpenoids, and organosulfur compounds [4]. In addition, several other compounds can be considered bioactive such as amino acids, hormones, polysaccharides, and fatty acids [8]. Figure 1 shows the main classifications of bioactive compounds as well as an example for each classification showing the general chemical structure.

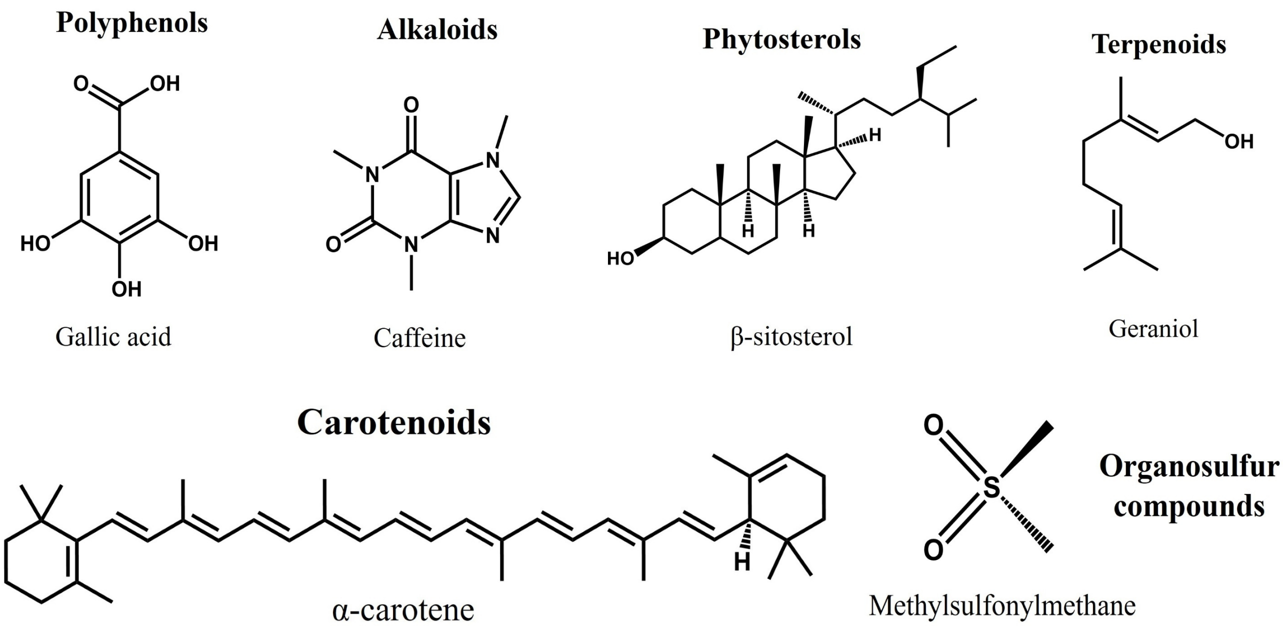

Figure 1. Classification of bioactive compounds

Given the increase in agro-industrial waste in recent years as food production keeps increasing to satisfy the global population, several studies have focused on obtaining high-value bioactive compounds from these wastes. Conventional techniques such as maceration, infusion, and distillation involve the use of ethanol, water, glycerol, acetone, hexane, and isopropanol. These solvents are considered highly toxic to the environment; emerging technologies such as microwave-assisted extraction, ultrasound-assisted extraction, and supercritical fluids, have been key to this purpose [9, 10]. It has been demonstrated that bioprocesses such as solid-state fermentation (SSF), submerged fermentation (SF), and liquid fermentation (LF) can be useful in the recovery of bioactive compounds [11, 12].

Bioactive compounds are a great source of biological activities, Martins et al. [13] highlight the relevance of SSF as a bioprocess for the recovery of phenolic compounds, in this regard the technique has gained great attention in recent years due to its potential for the revalorization of agro-industrial wastes for its low-cost and availability. Although it is crucial to understand the factors that operate in the production and/or recovery of phenolic compounds by SSF, that is why this review article aims to demonstrate better ways to recover and produce bioactive compounds by continuous and discontinuous production by SSF and their important biological activities.

Polyphenols with biological activity

Polyphenols are bioactive compounds found in a wide array of plants, and they offer important roles in health and therapeutics. Phenolic compounds present in plants may vary in quantity depending on the type of plant and organ being examined, due to genetics, maturity of the plant, and the climate where it grew [14]. These compounds can protect the plants from UV solar radiation and combat oxidative stress, potentially helping the plant to defend itself from pathogens and other factors [15].

Polyphenols can be found in many foods, including but not limited to, onions, broccoli, cauliflower, pomegranate, mango, raspberries, almonds, rice, oats, wine, tea, beer, and cider [16]. To obtain these compounds various conventional technologies are used combining the use of solvents such as ethanol, methanol, acetone, and hexane; the use of emergent technologies such as supercritical fluid extraction, microwave and ultrasound-assisted extraction, electric pulses, and bioprocesses such as SSF and SF are taking a great deal of importance in replacing the previously mentioned methods, as this methods can use water and ethanol as solvents and do not require the use of any harmful solvent [17, 18].

There are different types of polyphenols according to the composition of their functional groups, and these compounds range from simple and small molecules to large and complex compounds. Most polyphenols have benzene rings ($C6H6$) and various hydroxyl groups (–OH) allowing them to bind together with other molecules such as simple and complex sugars, amines, fats, carboxylic and organic acids, and some biomolecules that are soluble and insoluble in water [15, 19].

These compounds possess a molecular weight of around 500 to 3,000 Daltons. So far at least 8,000 types of polyphenols have been reported in the literature, and they have been classified into different categories, some of them are phenolic acids, flavonoids, lignans, stilbenes, and tannins. Figure 2 shows the classification of polyphenols and some examples of them [20].

Polyphenols are in charge of protecting the plant, fruit, or leaf from microbial and viral infections, defending it against ultraviolet radiation, and can also accomplish the task of attracting pollinators such as bees, bumblebees, and hummingbirds. These functions that are given to the plant can be translated as benefits for human health when they are consumed [21].

As they are of plant origin, they are found in dietary sources they are an important part of a balanced diet assuming a person consuming them has good eating behaviors. Regular consumption of these bioactive compounds has been demonstrated to protect against some diseases such as cardiovascular disease (CVD), diabetes, cancer, and even neurodegenerative diseases like Alzheimer's and Parkinson's [22–24].

There is a wide array of compounds in all families of bioactive compounds and many biological activities are linked to them.

Flavonoids

Flavonoids, as well as other polyphenolic compounds, are found commonly in plant-derived material, fruits, seeds, leaves, and even the bark of some trees, they can apport distinctive colors, and pleasant smells and alter the flavor of the foods that compose them. Common flavonoids like catechin, epicatechin-gallate, quercetin, and naringenin can be found in many easy-to-find foods such as chocolate, green tea, apples, cheery, grape, tomato, broccoli, red wine, orange, grapefruit, and lemons [25].

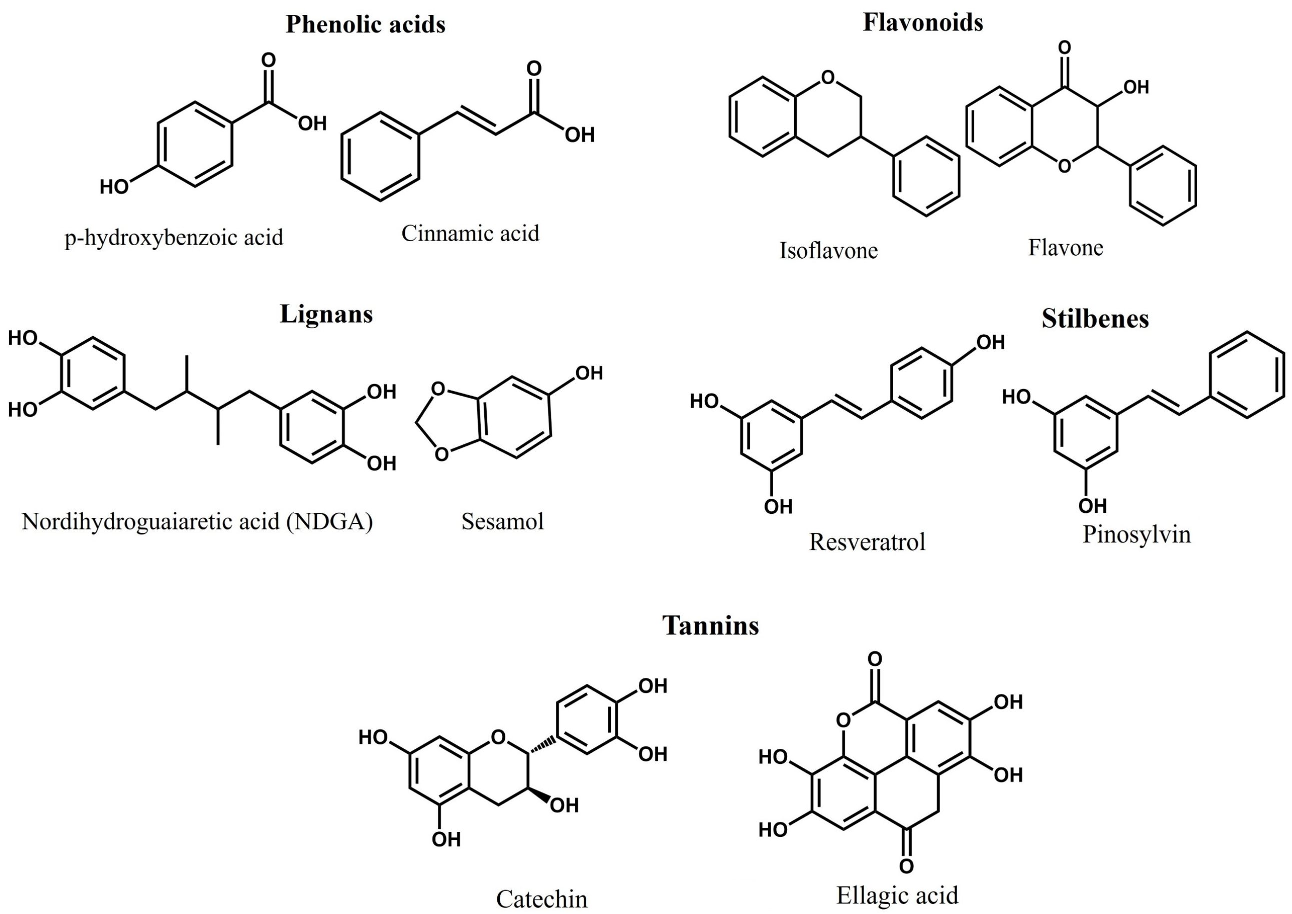

Figure 2. Classification of polyphenol compounds

Epicagallotechin-gallate (EGCG) is the main flavonoid found in green tea and matcha and it is known to confer this beverage which is widely popular in many countries of Asia many properties such as antioxidant, antiproliferative, antidementia, anti-inflammatory, and cardioprotective [26–28]. Recently with the surge of COVID in the year 2020, the search for answers on how to prevent and treat the disease led to the importance of studying previous molecules that could possess antiviral activity, EGCG has proven to be a potential source to inhibit SARS-CoV-2 virus. A study by Henss et al. [29] determined that EGCG was able to inhibit the replication of certain viruses with treatments of various concentrations of EGCG, the analyzed virus were the following; SARS-CoV-2 had an infection rate diminished by 50% (IR_{50}) with concentrations of 1.73 μg, MERS-CoV had an IR_{50} of 4.64 μg and lastly SARS-CoV had an IR_{50} of 0.83 μg.

Quercetin is a phenolic compound found in many natural sources, some of which are fruits and vegetables, some examples include grapes, onions, and apples, but this does not mean that quercetin is only found in food sources, it can also be found in medicinal plants previously used in folklore medicine some examples of medicinal plants are *Ginkgo biloba* and *Hypericum perforatum* [30]*.* This compound possesses various biological activities which grant consumers, antioxidants, antimicrobial, antitumoral, antidementia, anti-inflammatory, and cardiovascular protection [27, 31, 32].

Ellagitannins

Ellagitannins are dietary compounds found in many food products, such as teas, fruits, nuts, and even medicinal herbs. Ellagitannins can be found as geraniin and corilagin, and when digested or hydrolyzed can form ellagic acid [33, 34]. Ellagitannins possess a unique property that when completely digested by the gut microbiota can form urolithins. This is a complete indication that ellagitannins the compounds were fully taken advantage of and metabolized by the body [35]. Investigations on urolithins determined their multiple benefits to human health, one of which is the prevention of brain and neuronal damage, thus possibly preventing Alzheimer’s disease [36].

Geraniin is an ellagitannin commonly found in some medicinal plants and fruits. Geraniin has been studied previously for its great antioxidant, anti-inflammatory, antihypertensive, antiproliferative, and anticarcinogenic properties [33, 37–39]. Geraniin has demonstrated the potential as a great regulator for the angiotensin-converting enzyme (ACE), which regulates Angiotensin I and II responsible for elevating blood pressure, this molecule takes great importance due to the side effects that could occur with the consumption of current ACE inhibitors, the study used various concentrations of geraniin ranging from 0.1, 0.005, 0.001, 0.0005 and 0.0001 μM these concentrations was shown to positively inhibit the activity of ACE by 55%, 75%, and 75% showing an antihypertensive activity with potential of using it with patients [40].

Ellagic acid is the result of the hydrolysis of ellagitannins such as geraniin and corilagin, but this does not mean that it cannot be found in natural food sources, pomegranates, rambutan, and various kinds of nuts possess this biological compound [41]. Ellagic acid has a lot of bioactivities as an antioxidant, antimicrobial, antifungal, anti-inflammatory, neuroprotective, and cardiovascular protection factor, among others [42–46]. This molecule has been studied as an antidiabetic compound, studies in mice by Yang et al. [47] who administered an amount of ellagic acid equivalent to 0.1% of the weight of the mice to its diet with results showing that the compounds present in the diet of the mice helped lower the blood levels of glucose and also lowering triglyceride content. Ellagic acid also functions as a gene regulator, studies by Cisneros-Zevallos et al. [48] using ellagic acid at a concentration of 50 μM every 24 h decreased lipid accumulation by lipogenesis regulation, GLUT 4 glucose transporter and adiponectin. This shows the potential of ellagic acid as a regulator in metabolic disease, one of the current pandemics in the world that has until this point not been treated as it should be.

Carotenoids

Carotenoids are natural pigments that give vegetable sources their characteristic warm tones (orange, red, and yellow) [49]. These pigments not only give color naturally to our food preparations but can also provide the consumer with various biological activities such as antioxidant, anticancer, anti-inflammatory, antimicrobial, antifungal, antiviral, antiproliferative, and cardioprotective which are of interest to the whole population [50–54]. Some natural food sources of carotenoids include microalgae, mango, orange, papaya, pumpkins, watermelon, tomatoes, peppers, eggs, liver, crustaceans, and seafood in general [55].

A great characteristic of carotenoids is that not only plants can produce them, but some fungi, yeasts, and bacteria can produce them as a by-product of their fermentation [56]. Carotenoids have a key role in human health as a precursor for vitamin A (retinol), which has a greater biological role than what it is known for popularly by allowing us to see better, but it can also help in the differentiation, proliferation, and apoptosis of human embryonic stem cells [57].

Alkaloids

Alkaloids are natural compounds characterized for having a nitrogen molecule in any position of the structure. They are commonly found in plants, but can also be found in animals, insects, and some microorganisms [58]. The biological activity that alkaloids possess can be very important for the treatment of diabetes, cancer, and Alzheimer's disease [59–61]. Regarding the anticancer effect of alkaloids, vinblastine, vincristine, vindesine, and vinorelbine have anticancer effects against breast carcinogenic cells like MCF-7 and MDA-MB-231, hepatic cancer cells HepG2, HepG2/ADM and leukemia cells of K562 [62].

Solid state fermentation

SSF is a process in which microorganisms can grow on a substrate with a low amount of free water content. This process has been used ever since ancient times to produce food, antibiotics, enzymes, and biopesticides [63, 64]. SSF has several advantages such as low sterility requirements, lower water demand, and high-volume production and it can be used to grow aerobic and anaerobic microorganisms [65]. *Aspergillus oryzae*, *Trichoderma harzianum*, *Penicillium purpurogenum*, *Aspergillus niger*, and *Saccharomyces cerevisiae* are some microorganisms that produce bioactive compounds [66].

Two types of SSF have been defined, one where the microorganism grows on an organic material, an example of this being agro-industrial waste, which by extension contains a lot of nutrients not exploited by lack of consumption, and the second one where the microorganism develops on an inert material such as polyurethane foam (PUF), that when impregnated by liquid medium it can facilitate microbial growth [67, 68].

Although SSF faces a great challenge, industrial scalation involves the use of different mechanisms of action such as moisture, temperature, water activity, pH, microorganisms, heat, mass transfer, and oxygen availability. However, it is important to choose the appropriate conditions to recover and purify the product obtained [69, 70].

Factors of solid-state fermentation

Inoculum and microorganisms

Inoculum can be defined as a population of cells or spores supplemented to a fermentation medium to initiate said process, it must also be active and can adapt to the environmental conditions present in the culture medium [71]. SSF relies heavily on filamentous fungi, followed by yeasts and bacteria. Microbial growth hinges on two key nutrients: a carbon source for energy and structural properties, found in nutrients such as simple sugars or complex carbohydrates like starch, and a nitrogen source for protein synthesis [72].

Other factors that can alter the growth of microorganisms are the morphology and physiology of the microorganism, pH, chelating agents, presence of solids in the medium, viscosity, and temperature [73]. Nevertheless, using large amounts of inoculum can rapidly deplete available nutrients, affecting cell development and, consequently, product formation. Usually, values between 10^5 and 10^7 cells or spores per gram of fermentation medium are used [74].

Crafack et al. [75] mentioned that the physiological state of the inoculum directly impacts secondary metabolite production. A less-than-ideal state can significantly reduce output.

Temperature

Temperature is an important factor in SSF, as enzymes and other metabolites are sensitive to temperature [76]. High temperatures can damage enzymes and disrupt the production of desired compounds. Most importantly each microorganism has an optimal temperature range for growth [77]. The temperature has a great effect on the development of microorganisms as heat can effectively inhibit the growth when applied without a care in SSF, as it can cause the sudden death of the microorganism being used, also the sudden change of temperature [78] can the death of the microorganism used in SSF [79]. Cerda-Cejudo et al. [80] evaluated different factors, including temperature, using a central composite design for the production of ellagic acid by SSF with *Aspergillus niger* GH1 and demonstrated that this compound was obtained at temperature of 28.2°C.

Substrate

Agro-industrial wastes such as coffee pulp and husk, sugarcane and agave bagasse, fruit pulp and husks, and corn cobs, can be used as support or substrates to produce high-added value compounds [81]. These residues are abundant and are discarded as they have no specific use [82]. However, they can be used to extract polyphenolic compounds that possess commercial applications. Two types of solid matrixes are used in SSF: a nutritive matrix that provides nutrients to microorganisms such as starch, lignocellulose, and chitin, and a non-nutritive matrix which are matrixes that do not provide nutrients to microorganisms but can be used to infuse nutrients such as PUF and polystyrene [67, 78].

pH

The pH is a critical physicochemical parameter that influences SSF. pH is a determinant in the evaluation of microbial growth as it has a great influence due to the natural characteristics they need to reproduce. Each microorganism has a minimum pH rate, optimal, and maximum. Bacteria prefer a neutral pH, while fungi and yeasts prefer a slightly more acidic pH [72]. The natural metabolism of the microorganism may alter the conditions of the pH as it could decrease when the microorganism produces organic acids and increase with the alkalinization of urea [83].

Moreover, pH fermentation medium impacts directly on the metabolism of microorganisms, influencing biochemical reactions of catabolism and anabolism cells [74]. However, pH monitoring and control in SSF presents difficulties due to the absence of appropriate equipment and electrons to measure pH in solid materials and the existence of pH gradients due to the heterogeneous characteristics of SSF [84]. Polania Rivera et al. [85] observed an increase in polyphenols due to optimal conditions used in SSF process, including pH of 5.5 using *Rhizopus oryzae*.

Moisture and water activity

Water is an important parameter that influences the SSF process. The amount of water in a material is referred to as water content. Furthermore, water is essential for microbial growth and performs vital biological functions. It acts as a solvent, providing soluble nutrients and helping to remove metabolic waste. Additionally, it has a structural role, crucial for the stability and operation of biological structures at the molecular and cellular levels [84].

However, high levels of moisture will hinder the transfer of oxygen to the particles, reduce the surface area of the fermentation medium, and increase the risk of contamination. Instead, insufficient moisture will alter the metabolism of microorganisms, decreasing the transfer of nutrients and metabolites [74].

Fungi require a moist environment to grow, such as *Aspergillus niger* GH1, HT3, or PSH [86]. Inadequate water content can hinder the uptake of nutrients by microorganisms, which can affect their growth. An optimum moisture content for microorganism growth and substrate utilization is between 40 and 70% [69, 72]. De La Rosa-Esteban et al. [87] demonstrated the accumulation of ellagic acid via SSF with *S. cereviasiae* using a 60% moisture, 30°C and 1.5×10^7 cells/g.

Process to produce bioactive compounds through fermentation

Continuous process

A continuous process is when materials or energy move uninterruptedly through a system. These processes are widely used in industries, and an example of this is in food production, in addition to offering several advantages such as efficiency, high productivity, and control. However, the continuous process presents some challenges such as higher complexity and costs [88].

SSF is adapting to continuous processes, which makes SSF more cost-effective, as continuous processes are more efficient and require fewer resources [89]. SSF has several challenges, one of them is the scale at the industrial level, and within this is the choice of the bioreactor which is the environment in which microorganisms grow and are activated [90].

The bioreactor is fundamental in the development of bioprocesses, with various types used in fermentation technologies for the production of secondary metabolites, such as bioactive compounds [91]. Most SSF bioreactors operate in batch mode, however, some effects have been to design SSF systems capable of continuous operation. One of the bioreactors that have been adapted to a continuous system is a packed bed reactor (PBR) or column-type bioreactor [74]. This type of bioreactor consists of columns where the solid substrate is supported on a perforated base, allowing air to be forced through the substrate [92].

PBR has several multiple advantages, such as simple handling, larger bed volume, and easy scale-up, in addition, they can support microbial growth for long periods of culture under low shear conditions due to the immobilization of cells within microporous matrices [90, 93].

Now, few studies report continuous bioactive compound production, however, Buenrostro-Figueroa et al. [94] reported that ellagic acid could be continuously produced from pomegranate peel ellagitannins employing a PBR with *Aspergillus niger* GH1 under ideal conditions. In contrast, Taavoni et al. [95] reported the continuous production of B-carotene using *Rhodotorula rubra* cells in an airlift bioreactor, employing fatty acids from soap waste as a carbon source.

Discontinuous process

The discontinuous process often uses a batch process, which is carried out as its name implies, in batches and is a technology suitable for SSF, so it can be carried out in trays, containers, etc. [96]. In this type of process, the microorganism that is used must be inoculated in a fermented substrate with a fixed volume, therefore, the culture medium needs to be sterilized and changed with each fermentation. Once the fermentation time is done, the result will be the biological compounds of interest that can be accumulated and recovered [97]. A batch process is easy to implement as it requires low costs, the sterilization process is not as complicated, can be easy to handle, has greater flexibility, and has a very low risk of contamination. The main disadvantages are that it has lower productivity compared to the continuous process, the process control is lower, and a higher waste generation is presented [97, 98] (Table 1).

Table 1. Characteristics of continuous vs discontinuous processes [99, 100]

Characteristics	Continuous process	Discontinuous process
Process operation efficiency	Can maintain constant production.	The batch system has challenges due to conditions over time and process control.
Yield and productivity	Offers greater productivity.	Reduce productivity due to SSF factors, which may result in lower yields and undesirable products.
Microbial growth and sporulation	The continuous system can be designed to optimize the fermented material to obtain an adequate growth of microorganisms.	Environmental conditions may affect microbial growth; thus, a lower biomass rate may result.
Substrate	Substrate addition is done continuously during the process.	At the beginning of the process, the substrate is added and no more is needed.

Some studies that evaluate the recovery of bioactive compounds using SSF through a batch process can be traced back to the study of Polania Rivera et al. [85] whose research group evaluated SSF applying a batch process using aluminum trays and the resulting compounds identified the polyphenols such as gallic acid, caffeic acid, and cinnamic acid. Coronado-Contreras et al. [86] determined the content of hydrolyzable and condensed tannins (3.5 mg/g and 32.9 mg/g respectively) from prickly pear peel using SSF and using *Aspergillus niger* GH1 and HT3 as microorganisms, as well as demonstrating high antioxidant activity.

Conclusions

SSF offers a promising approach for recovering bioactive compounds from agro-industrial waste. While traditional batch processes are simple and cost-effective, they often show inconsistent recovery of bioactive compounds. To address this limitation, researchers are exploring continuous SSF methods for higher efficiency and profitability. This shift towards continuous processing needs the development of suitable bioreactors. Packed bed bioreactors, recognized for their scalability and straightforward scale-up process, have demonstrated potential in the continuous production of ellagic acid. In the last decade, the need to generate bioprocesses that allow continuous or discontinuous production of bioactive compounds has been identified, since the extraction processes have been extensively studied, further research on continuous. SSF is crucial to unlock the potential of this method for broader polyphenol production across the food, pharmaceutical, and cosmetic industries, leveraging the diverse health benefits these compounds offer.

Abbreviations

ACE: angiotensin-converting enzyme

EGCG: epicagallotechin-gallate

PBR: packed-bed reactor

PUF: polyurethane foam

SF: submerged fermentation

SSF: solid-state fermentation

Declarations

Acknowledgments

The authors thank the School of Chemistry, Autonomous University of Coahuila.

Author contributions

KDLRE: Conceptualization, Investigation, Writing—review & editing. LS, JJBF, and CNA: Validation, Resources, Writing—review & editing. MLCG, LEEG, and ASG: Validation, Writing—review & editing. JAAV: Conceptualization, Supervision, Resources, Validation, Investigation, Writing—review & editing.

Conflicts of interest

Cristóbal N. Aguilar who is the Editorial Board Member of Exploration of Foods and Foodomics had no involvement in the decision-making or the review process of this manuscript. The other authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

The author Karen De La Rosa-Esteban thanks SECIHTI México for scholarship support. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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