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Literature review paper

Bioactive compound production via solid-state fermentation: emerging opportunities

Producción de compuestos bioactivos mediante fermentación en estado sólido: oportunidades emergentes

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Abstract

The natural environment is an extraordinary reservoir of microorganisms that generate compounds with significant pharmaceutical relevance. Over the past decades, numerous companies have successfully exploited these microorganisms, primarily through submerged fermentation, to obtain antibiotics, enzymes, and other bioactive molecules. However, submerged fermentation sometimes presents limitations regarding oxygen transfer, production yields, compound stability, foaming, and environmental impact. Solid-state fermentation is a more sustainable alternative technology because it can valorize agro-industrial byproducts as culture media and produce bioactive compounds, contributing to a circular bioeconomy. The pharmaceutical industry is seeking solutions to decrease the costs of production processes and enhance process sustainability, and solid-state fermentation

may provide exciting alternatives. However, challenges remain in scaling up, process control, and optimizing the recovery of bioactive compounds. This review highlights advances in bioactive compounds with potential pharmaceutical applications produced through solid-state fermentation, with particular emphasis on different classes, including antibiotics, biosurfactants, enzymes, polymers, vitamins, and aroma compounds. By addressing current limitations and showcasing innovative applications, solid-state fermentation is positioned as a viable complementary strategy for pharmaceutical bioprocesses.

***Keywords*: pharmaceutical industry, biological activity, byproducts, valorization, microbial compounds.**

Resumen

El entorno natural constituye una valiosa fuente de microorganismos capaces de producir compuestos de gran relevancia farmacéutica. Durante las últimas décadas, numerosas empresas han aprovechado estos microorganismos, principalmente mediante fermentación sumergida, para obtener antibióticos, enzimas y otras moléculas bioactivas. Sin embargo, este sistema de fermentación presenta limitaciones asociadas a la transferencia de oxígeno, los bajos rendimientos de producción para algunos compuestos y su estabilidad, la formación de espuma durante el proceso y su impacto ambiental. En este contexto, la fermentación en estado sólido surge como una alternativa más sostenible, ya que permite valorizar subproductos agroindustriales como sustratos y producir compuestos bioactivos, favoreciendo así el desarrollo de una bioeconomía circular. Dado que la industria farmacéutica busca reducir los costos y aumentar la sostenibilidad de sus procesos, esta tecnología ofrece oportunidades prometedoras. No obstante, aún existen desafíos importantes en cuanto a la escalabilidad, el control del proceso y la optimización de la recuperación de los compuestos producidos. Esta revisión presenta los avances importantes en la obtención de compuestos bioactivos con potencial aplicación farmacéutica mediante fermentación en estado sólido, con especial atención a diversas clases de productos, como antibióticos, biosurfactantes, enzimas, polímeros, vitaminas y compuestos aromáticos. Al analizar las limitaciones actuales y destacar aplicaciones emergentes, se posiciona a la fermentación en estado sólido como una estrategia complementaria y viable para el desarrollo de bioprocesos farmacéuticos más sostenibles.

***Palabras clave*: industria farmacéutica, actividad biológica, subproductos, valorización, compuestos microbianos.**

1. Introduction

Over the centuries, pharmaceuticals have provided many health benefits and improved the quality of human life. They consist of a large and varied group of organic compounds used for their specific biological effects. They penetrate cellular membranes, have a specific mode of action, and can persist in the body. Many pharmaceuticals, such as analgesics, antibiotics, antiepileptics, β-blockers, blood-lipid regulators, antidepressants, anxiolytics, sedatives, contraceptives, steroidal hormones, antineoplastics, and antitumor agents, have been produced and sold worldwide (Salehi & Rashidinejad et al., 2025). The pharmaceutical sector is one of the fastest-growing industries, with a global market worth over a trillion USD (Brekke et al., 2025).

Biotechnology has improved the production of biological pharmaceuticals in the market, such as monoclonal antibodies (e.g., trastuzumab deruxtecan), cytokines, fusion proteins, therapeutic enzymes, recombinant vaccines, blood factors, hormones, and growth factors (Inoue et al., 2020). The above statement can be associated with products that show advantages over synthetic drugs, such as better selectivity, lower toxicity, milder side effects, and being more environmentally friendly (Inoue et al., 2020). Generally, the microbial bioactive compounds are produced by submerged fermentation (SmF), such as steroids (prednisolone, 11-α-hydroxy-progesterone), intermediate compounds (citric acid, fumaric acid), antibiotics (penicillin, cephalosporin, cordycepin), antifungals (polynes), antivirals (Shikimic acid (precursor of oseltamivir), and antiparasitic (avermectins) (Ma et al., 2023). Many studies have highlighted higher yields of bioactive production when solid-state fermentation (SSF) is involved (Kumar et al., 2021), which can be attributed to more significant biomass growth and oxygen availability. For instance, the commercial production of statins and related substances prefers SSF because of its low media cost, product stability, increased product yield, and increased porosity (Valdés-Velasco et al., 2022).

The trends in scientific research papers and patent documents on solid-state fermentation in pharmaceutical applications are as follows. Research papers were searched in the Scopus® database (www.scopus.com) containing the words (solid AND state AND fermentation AND pharmaceutical or health or pharmacy or medical) in the title, abstract, or keywords, from 2014 to present, resulting in 772 documents. A huge linear increasing trend was observed for the number of papers. The increase was about 75 %. Patent documents were searched in the Lens database (www.lens.org) containing the words (solid AND state AND fermentation AND pharmaceutical) in the keyword or patent field from 2014 to 2024. Around 39851 patent records were found. Therefore, there has been growing interest in this topic over the last 10 years.

This review focuses on bioactive compounds obtained through a specific fermentation technique, SSF, which has shown higher product yields using low-cost substrates than submerged fermentation does. The generalities, benefits, and challenges of the SSF are described in Section 2. Bioactive compounds, including antibiotics, aromas, biosurfactants, polymers, enzymes and vitamins, and their related SSF production are presented in Section 3. Finally, Section 4 presents the conclusions and perspectives of this review.

2. Benefits and challenges of solid-state fermentation

SSF is a microbial culture technique involving the growth of microorganisms on a solid medium in the absence or near absence of free water runoff (Cordero Soto et al., 2025). Water plays an essential role in biological processes, and is absorbed into solid surfaces, where it can be present in the form of a thin film (Valdés-Velasco et al., 2022). Fermentation of solid materials is an ancient technology that has been used since antiquity to produce food. It is widely used in East Asian countries to prepare food on an industrial scale. In contrast, SmF is the preferred for the industrial production of microbial value-added compounds in the West (Cordero Soto et al., 2025). The main reason for this is the heterogeneous nature of the solid medium, which impedes the efficient monitoring of the process, such as temperature, pH, moisture, and substrate concentration, whereas SmF has precise online monitoring devices.

SSF holds tremendous potential for producing microbial compounds compared to SmF. The main advantage of SSF is the possibility of using agro-industrial byproducts as a solid medium. These byproducts are massively overproduced worldwide and still contain an exciting level of nutrients that enable microbial growth (Chilakamarry et al., 2022; Tripathi et al., 2024). The valorization of these wastes through SSF increases the sustainability of the process. From an economic perspective, their use lowers global costs because they are inexpensive, whereas synthetic carbon and nitrogen sources account for a substantial part of the worldwide cost (Costa et al., 2021). Regarding the environmental aspect, this valorization mitigates the negative impact on the environment that may otherwise result from improper waste management, especially in the case of byproducts containing toxic compounds (Mahanta et al., 2008). Finally, this aligns with increasing public expectations regarding the natural origin of products, whether related to the health, cosmetics, or food industries (Cordero Soto et al., 2025).

Regarding raw materials, the requirement for SSF is usually lower, leading to a cheaper initial investment. In addition, low water content usually causes the SSF bioprocesses to have lower surface area occupation and does not require downstream effluent treatment, which impacts the overall cost (Valdés-Velasco et al., 2022). This is always the case, as some SSF processes for enzyme production may require the same amount of water to extract the enzyme, which can be similar to the total water content used in SmF processes. Table 1 presents the main advantages and disadvantages of solid-state fermentation (SSF) and submerged fermentation (SmF) for the production of bioactive compounds.

Table 1. Comparison between Solid-State Fermentation and Submerged Fermentation.
Tabla 1. Comparación entre la fermentación en estado sólido y la fermentación sumergida.

Criterion	Solid-State Fermentation	Submerged Fermentation	Reference
Process control	Limited; difficult control of temperature, pH, and oxygen	High; easy monitoring and control of pH, temperature, and aeration	Cordero Soto et al., 2025
Oxygen transfer	Generally suitable for aerobic microorganisms, but difficult to regulate	Efficient and controllable through agitation and aeration	Mehmood et al., 2022
Water consumption	Low	High	
Operational cost	Generally lower	Higher due to equipment, energy use, and process control	
Scalability	More complex and limited at industrial scale	High; widely applied at industrial scale	
Contamination risk	Lower due to low water activity	Higher due to liquid medium	
Product recovery	More complex; requires additional downstream steps	Easier through filtration or centrifugation	

2.1 Oxygen

The reduced availability of free water in SSF enhances oxygen transfer, thereby promoting microbial growth (Banat et al., 2021; Valdés-Velasco et al., 2022). Oxygen transfer depends on the

available interfacial gas-liquid surface area and the thickness of the wet fungal layer. Besides, SSF describes resistance to phenomena of catabolite repression and substrate inhibition. Hence, enzymes are usually produced in higher yields than those observed in SmF using elevated concentrations of simple sugars with relatively low levels of inducers (Valdés-Velasco et al., 2022).
Despite these benefits, substrate uptake and biomass quantification are challenging because of the close interaction between microorganisms and the solid medium, although indirect methods such as respirometry monitoring for biomass determination may be used.

2.2 Temperature

Another aspect of the solid substrate is its porosity and the formation of mass and heat gradients due to the poor transfer coefficients of the solid matrix, which may lead to the accumulation of heat and gases inside the bioreactor bed, especially at higher production scales (Cordero Soto et al., 2025).

Heat transfer is important because microorganisms often grow in specific temperature ranges, and the fermentation process generates metabolic heat. Different strategies exist to overcome this issue, resulting in a wide diversity of bioreactor designs (Krishania et al., 2018). Two main strategies exist that can be used in combination. The first strategy is based on the forced aeration of moist air through the bed to remove heat, carbon dioxide, and volatile substances through convection (Mehmood et al., 2022). In addition, the water evaporation process, an endergonic reaction, allows efficient heat removal but requires water replenishment, which can be carried out through aeration with water-saturated air (Mehmood et al., 2022). Granulometry and the compressibility index are also key parameters for enhancing the heat transfer (Oiza et al., 2022). The other strategy is agitation, which can release nutrients and impair the formation of gradients, but can disrupt microbial cells, especially in the case of filamentous microorganisms. These damages can be mitigated by modulating parameters such as the frequency and speed of agitation and the type of agitation system, that is, baffles, padded, or rotating drum (Robinson & Nigam, 2003; Finkler et al., 2017). Thus, for each agitated bioprocess, a careful study of the impacts of these parameters must be conducted to achieve a balance between mass and heat transfer gradients and cell disruption. Recent advances in mathematical modeling have led to a deeper understanding of SSF processes and may support the successful development and large-scale implementation of SSF production systems (Perez et al., 2019; Finkler et al., 2021).

2.3 Recovery of biomass and products

Downstream processes account for 70 % of the total production cost. They are not required if the fermented solid is used as a final product, such as conidia, for applications such as pesticides. Thus, bioprocesses have taken advantage of the economic benefits of SSF. However, if they are required, the use of solvents is common and sometimes not environmentally friendly, limiting the pharmaceutical applications of the obtained bioactive compounds and the reuse of solid waste. In addition, solvents can increase the production cost because of the high required volume, their prices, and energy consumption (Oiza et al., 2022). Bioproduct recovery depends on its physical and chemical characteristics, such as thermostability and pH resistance. Thus, alternative methods for bioproduct recovery with reduced environmental and economic impact include ultrasound-assisted

extraction, microwave-assisted extraction, supercritical fluid extraction, solid-liquid extraction, pressurized liquid extraction, subcritical water extraction, solid-solid extraction, and enzyme-assisted extraction (Oiza et al., 2022). However, optimization focused on downstream processes has not been widely studied and is fundamental to the total production cost and environmental impact of SSF.

3. Bioactive compounds obtained by solid-state fermentation

Microbial diversity is a tremendous source of bioactive compounds whose applications range from antimicrobial, antioxidant, and immunomodulatory activities in various critical industries like drugs, healthcare, surgical devices, food preservation, and packaging, to name a few. In the specific case of antimicrobial activities against pathogenic agents, and notably because of the appearance of resistant pathogenic strains to systemic antibiotics, the search for new antimicrobial compounds is of primary importance in the chemistry and biotechnology sectors (Varghese et al., 2020). In this context, the focus has been on antibiotics, biosurfactants, polymers, aromas, enzymes, and vitamins (table 2).

3.1 Antibiotics

Antibiotics are biologically active compounds produced by microorganisms as a defense mechanism to stop or selectively inhibit the growth of other microorganisms. Antibiotic production has been investigated in the last decades using alternative economic sources, such as agro-industrial byproducts, using SmF and SSF (De la Cruz-Quiroz et al., 2019; Zeng et al., 2022). Several factors must be considered, including environmental and biological aspects, physiological characteristics of the microorganisms, and their optimal growth culture (De la Cruz-Quiroz et al., 2019).

Cephalosporin-C (Fig. 1A) was produced in comparable quantities as a secondary metabolite through SSF and SmF. In the case of SSF, sugarcane bagasse was used as a solid medium (Tabaraie et al., 2012). Other studies have reported antibiotic production by SSF, such as the extracellular antibiotic rifamycin B (Fig. 1B), produced by *Amycolatopsis Mediterranean* MTCC 14 from agro-industrial byproducts (Vastrad & Neelagund, 2012). The results of this study showed that ground nutshells and coconut oil cake presented higher yields of antibiotic production than those obtained with groundnut oil cake and rice husks. Paromomycin (Fig. 1C) is an effective antibiotic for treating Gram-positive and Gram-negative bacteria, protozoa, mycobacteria, and numerous antibiotic-resistant pathogens. It is produced by *Streptomyces rimosus* subsp. *paromomycinus* NRRL 2455 through SSF using corn bran impregnated with aminoglycosides as the growth medium (El-Housseiny et al., 2021). Cephamycin C antibiotic production by *Nocardia lactamdurans* was evaluated in SSF using soybean flour with a moisture content of 65 % at 28 °C and an initial pH of 6.5. The maximum cephamycin C production under these conditions was 15.75 mg (g dry solid)$^{-1}$ (Kagliwal et al., 2009). Henceforth, a gram of dry solid (gds). Other necessary antibiotics produced as secondary metabolites during fermentation include penicillin, neomycin, puromycin, cephabacin, nocardicin A, actinorhodin, enterocin, tetracenomycin, actinomycin, carbomycin, erythromycin, and tetracycline (Kumar et al., 2021; Zeng et al., 2022).

Antibiotic production by biotechnological processes, such as SSF, generally involves the use of a complex medium that may decrease the overall purity of the compound. However, extraction and

purification strategies to obtain high-grade metabolites have been continuously studied to overcome this limitation.

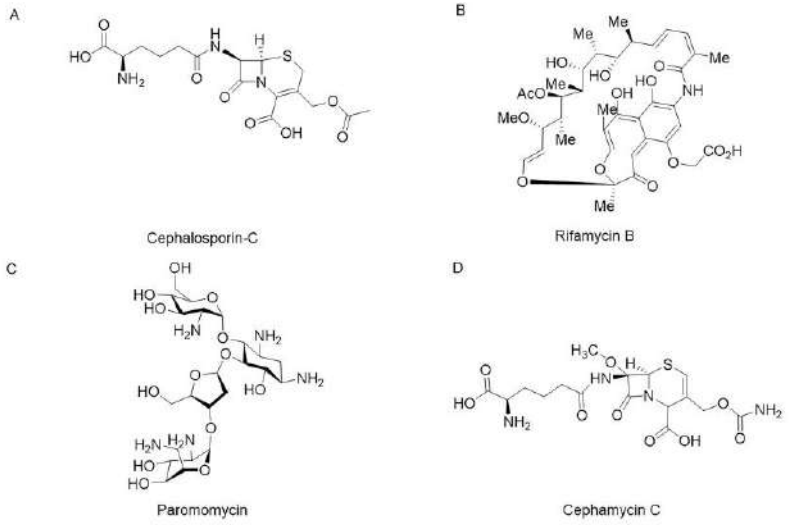

Figure. 1 Chemical structures of antibiotics produced by SSF. A) Cephalosporin-C. B) Rifamycin B. C) Paramomycin. D) Cephamycin C.
Figura. 1 Estructuras químicas de antibióticos producidos por SSF. A) Cefalosporina C. B) Rifamicina B. C) Paromomicina. D) Cefamicina C.

3.2 Aroma compounds

Aroma compounds are molecules naturally obtained from plants, seeds, and fruits, or through biotechnological processes using microorganisms or isolated enzymes. Their natural production has been strongly performed in the last two decades developing fermentation systems, mainly by SmF (Cordero-Soto et al., 2025). Nevertheless, other approaches, such as SSF, have been proposed for by-product valorization and aroma production (Hadj Saadoun et al., 2021), especially those showing novel applications in the pharmaceutical industry and medical treatments (Arya et al., 2021).

The natural aldehyde 4-hydroxy-3-methoxybenzaldehyde (Fig. 2A) is the main compound in the extract obtained from the pods of the *Vanilla planifolia orchid* (Arya et al., 2021). This compound, named vanillin, has a sweet flavor and delicate floral fragrance, properties that the food and cosmetic industries have been searching for to increase the quality of their products (Palmerín-Carreño et al., 2019). However, in the last decades, its medicinal and biological properties have been investigated (Arya et al., 2021). Vanillin exhibits antioxidant, anticarcinogenic, anti-inflammatory, anti-apoptotic, neuroprotective, and anti-stress biological activities (Ueno et al., 2019). The consumption of vanillin in a designed high-fat diet for obese mice revealed promising results in reducing adipose tissue and glucose metabolism, among other benefits (Martău et al., 2021). In addition to its intake, vanillin has also been studied in alternative medicine and aromatherapy to elucidate its neuropsychological effects (Ueno et al., 2019).

With these novel applications and the high global demand for vanillin, efforts to obtain this compound through biotechnological processes have increased, as its direct extraction from plants is limited, and the vanillin obtained by microbial/enzymatic bioprocesses is considered a safe and natural source (Martău et al., 2021; Paul et al., 2021). In this sense, recent studies have been carried out by SSF to produce biovanillin. Mehmood et al. (Mehmood, Ahmed, et al., 2022) studied fruit byproducts with a high content of ferulic acid, including pomegranate, banana, and orange peels as substrates to produce biovanillin using *Enterobacter hormaechei*, reaching a maximum yield of 0.09 mg g^{-1} after 24 h of fermentation. Other food byproducts, such as sugarcane bagasse, wheat straw, corn cob, and rice bran and straw, were evaluated and selected according to their ferulic acid content and biovanillin production by SSF (Mehmood, Saleem, et al., 2022). The results showed that sugarcane bagasse is a promising substrate for producing biovanillin using *Enterobacter hormaechei* at 37.5 °C, pH 7.5, and a moisture content of 70 %.

Phenethyl alcohol (Fig. 2B), also known as 2-Phenylethanol (2-PE), is a higher alcohol with pleasant rose-like notes naturally found in plants and flowers. It is used in the pharmaceutical, cosmetic, and food industries as a preservative because of its efficient antimicrobial and antifungal activities (Martínez et al., 2018; Mierzejewska et al., 2019). 2-PE has been studied as an anti-depressant and anti-stress treatment through inhalation in mice (Ueno et al., 2019). Its biotechnological production has been mainly studied in SmF, especially by coupling in situ product removal techniques to avoid the inhibition of microorganisms. However, other approaches have been explored, such as using food byproducts to valorize or decrease the production costs (Martínez et al., 2018; Martínez-Avila et al., 2021). Soy fiber, rice husk, rice fiber, and apple pomace were evaluated as potential substrates for 2-PE bioconversion through SSF using *Pichia kudriavzevii*. Results showed that the highest 2-PE production (25.2 mg gds^{-1}) was obtained using red apple pomace as the substrate with L-phenylalanine (L-Phe) supplementation after 70 h (Martínez-Avila et al., 2021). The potential of sugarcane bagasse as a single carbon source, supplemented with L-phe, using *Pichia kudriavzevii* in an SSF process was evaluated and optimized, reaching a maximum 2-PE concentration of 27. 2 mg gds^{-1} (Martínez-Avila et al., 2020). Moreover, sugarcane bagasse was evaluated in SSF to produce 2-PE and its derivative ester, 2-phenethyl acetate (2-PEA) (Fig. 2C), a compound with similar properties and aroma (Martínez et al., 2018). L-phe was added to the media to trigger the Ehrlich pathway in *Kluyveromyces marxianus* yeast. The results showed that the system was adequate for producing 2- PE and its ester, 2-PEA ester (Martínez et al., 2018). Fig. 3 illustrates the mechanism for obtaining 2-PE and its ester, 2-PEA.

2-phenethyl acetate and several fruity aroma compounds, such as isoamyl acetate, decanoate, ethyl dodecanoate, and octanoate, were produced by *Saccharomyces cerevisiae* in SFF from orange peels (Mantzouridou et al., 2015). Lactones have also been obtained using SFF. Try et al. (2018) proposed a novel system based on an impregnated inert support (luffa sponge) using *Yarrowia lipolytica*; the results showed a high yield of 3-hydroxy-γ- decalactone (Fig. 2D). However, the biological activity and medicinal potential of these aroma compounds have been poorly studied, and their study has focused on their application as flavoring agents.

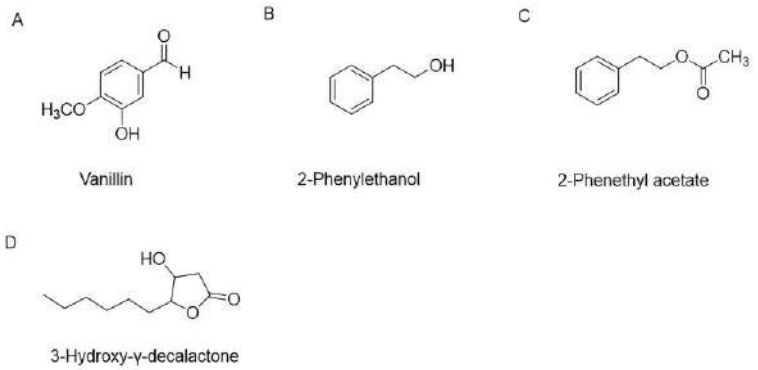

Fig. 2 Chemical structures of aromas produced by SSF. A) Vanillin. B) 2-Phenylethanol. C) 2-Phenethyl acetate. D) 3-hydroxy-γ- decalactone.
Fig. 2 Estructuras químicas de aromas producidos por SSF. A) Vainillina. B) 2-feniletanol. C) Acetato de 2-feniletilo. D) 3-hidroxi-γ-decalactona.

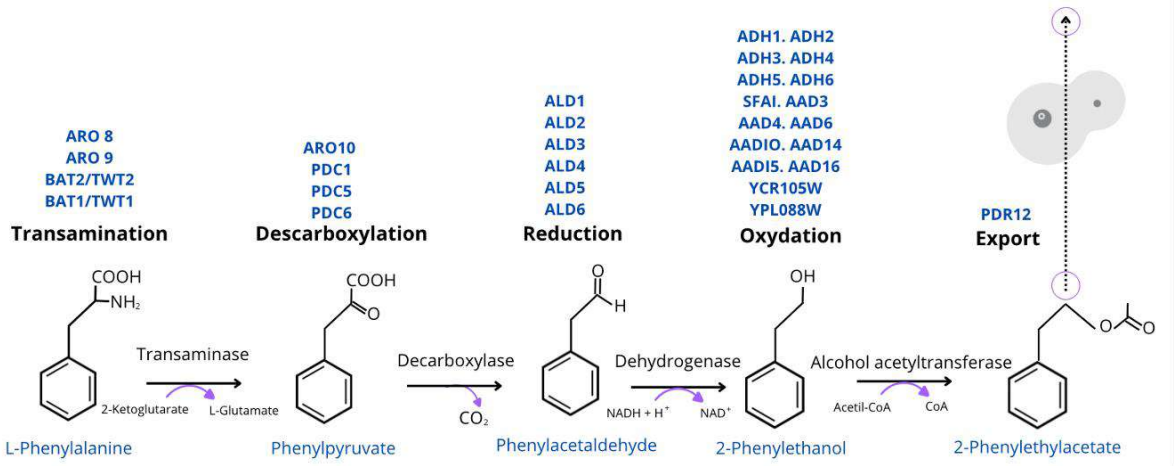

Fig. 3 Ehrlich pathway to produce 2-Phenylethanol and 2-phenylethylacetate.
Fig. 3 Ruta de Ehrlich para la producción de 2-feniletanol y 2-feniletil acetato.

3.3 Biosurfactants

Biosurfactants are amphiphilic compounds that reduce surface tension. Bacteria, yeasts, and fungi produce these compounds, with no reported side effects in humans (Wan et al., 2022). Their environmental toxicity is lower, and their resistance to extreme temperatures, pH, and salinity is higher than that of chemical surfactants (Ribeiro et al., 2020). A critical contemporary biological activity of biosurfactants is the inactivation of SARS-CoV2 by membrane disruption (Banat et al., 2021; Raza et al., 2022). However, large-scale biosurfactant synthesis is limited by its high production costs and low productivity (Banat et al., 2021). For instance, sophorolipids, one of the cheapest biosurfactants in the market, have a sales price estimated at approximately 32 USD Kg^{-1} versus 1-2 USD Kg^{-1} for a synthetic surfactant such as sodium lauryl sulfate (Dolman et al., 2019). Therefore, different strategies have been proposed to improve production, including the use of SSF. Indeed, in the case of lipopeptide synthesis, for example, a study showed that SSF, in comparison with SmF,

increased the production tenfold according to the evaluated strains compared to gL^{-1} (Valdés-Velasco et al., 2022). Moreover, because of the absence or near absence of free water, foam formation can be significantly reduced, which is an issue during biosurfactant production using SmF (Chen et al., 2021). Foaming may hinder the overall productivity of the process, requiring the addition of expensive antifoaming agents (Valdés-Velasco et al., 2022). The use of agro-industrial byproducts in SSF presents new challenges in downstream purification owing to the complex nature of the crude extract (Valdés-Velasco et al., 2022). Therefore, using an inert support such as polyurethane foam with an impregnated nutritional solution avoids these problems, facilitating product analysis, purification, control, and monitoring of the bioprocess (Jiménez-Peñalver et al., 2019). This strategy has been successfully used for glycolipid and lipopeptide production in SSF (Gong et al., 2020; Valdés-Velasco et al., 2022).

Biosurfactants are classified according to their structure into glycolipids, lipopeptides, phospholipids, polymerics, and particulates. Glycolipids have potential applications in the pharmaceutical industry because of their antimicrobial, anti-adhesive, antitumor, antioxidant, antiviral, immunomodulatory, enzyme-inhibitory, and insecticide effects (Varvaresou & Iakovou, 2015; Banat et al., 2021). Sophorolipids and rhamnolipids are representative glycolipid biosurfactants. Several studies have reported the production of sophorolipids (Fig. 4A) by SSF using agro-industrial residues as solid supports (Jiménez-Peñalver et al., 2019). For instance, sophorolipids produced by *Starmerella bombicola* (previously *Candida bombicola*) using a mixture of sunflower oil cake and crude soybean oil reached a yield of 0.5 g gds^{-1} and exhibited activity against cancerous cells in human tumor cell lines of hepatocellular carcinoma HepG2 and lung cancer A549 by inhibiting the activities of urokinase and histone deacetylase (Rashad et al., 2014). *Candida bombicola* NRRL Y-17069 also synthesized sophorolipids from sunflower oil cake reaching 0.48 g gds^{-1}. It showed a more efficient reduction in total cholesterol, low-density lipoprotein cholesterol, atherogenic index, liver transaminase activity, malondialdehyde, and antioxidant enzymes than rosuvastatin in male albino rats (Nooman et al., 2017).

Rhamnolipid (Fig. 4B) production by *Pseudomonas aeruginosa* attained a concentration of 6.25 μg ml^{-1} that was evaluated for its antiproliferative effects against human breast cancer cells (Varvaresou & Iakovou, 2015). The highest reported rhamnolipid concentrations in SSF are 41.87 to 45.4 g L^{-1} of the impregnating solution by *Pseudomonas aeruginosa* grown on a mixture of sugarcane bagasse and sunflower seed meal and a mixture of sugarcane bagasse and corn bran, respectively (Camilios-Neto et al., 2011; El-Housseiny et al., 2019).

The most studied lipopeptide biosurfactants are those produced by *Bacillus strains*, such as surfactin, iturin, and fengycin (Varvaresou & Iakovou, 2015; Valdés-Velasco et al., 2022). They were produced from millet by *Bacillus subtilis* SPB1 through SSF (20.8 mg gds^{-1}), showing broad-spectrum antimicrobial activity against microorganisms with a multidrug-resistant profile, such as *Staphylococcus aureus*, *Staphylococcus xylosus*, *Enterococcus faecalis*, *Klebsiella pneumonia*, *Escherichia coli*, and *Candida albicans* (Ghribi et al., 2012). *Bacillus cereus* SNAU01 generated lipopeptides using peanut oil cake under SSF, which had potential application as an anti-biofilm agent against *Pseudomonas aeruginosa* MTCC 2453 and *Escherichia coli* MTCC 2939 (Nalini et al., 2016). Surfactin (Fig. 4C) displays activity against herpes viruses and retroviruses because it inhibits membrane fusion between the virus and host cells, preventing the infection of epithelial cells (Varvaresou & Iakovou, 2015; Banat et al., 2021). Surfactin exhibits anticancer activity against several cancer types, including breast, colon, leukemia, hepatocellular, cervical, oral epidermoid, and pancreatic cancers (Wu et al., 2017). *Bacillus*

pumilus HY1 grown on soybeans as a solid support produced surfactin that inhibited the growth of cancer cell lines MCF-7 and Caco-2 at 100 μg L^{-1} (Hong et al., 2021).

Iturin (Fig. 4D) has broad-spectrum antibacterial, hemolytic, anticarcinogenic, and thrombolytic properties (Zhao et al., 2017; Wan et al., 2022). It was synthesized from soybean meal by *Bacillus velezensis* ND under SSF, showing significant potential for industrial production (Shen et al., 2025).

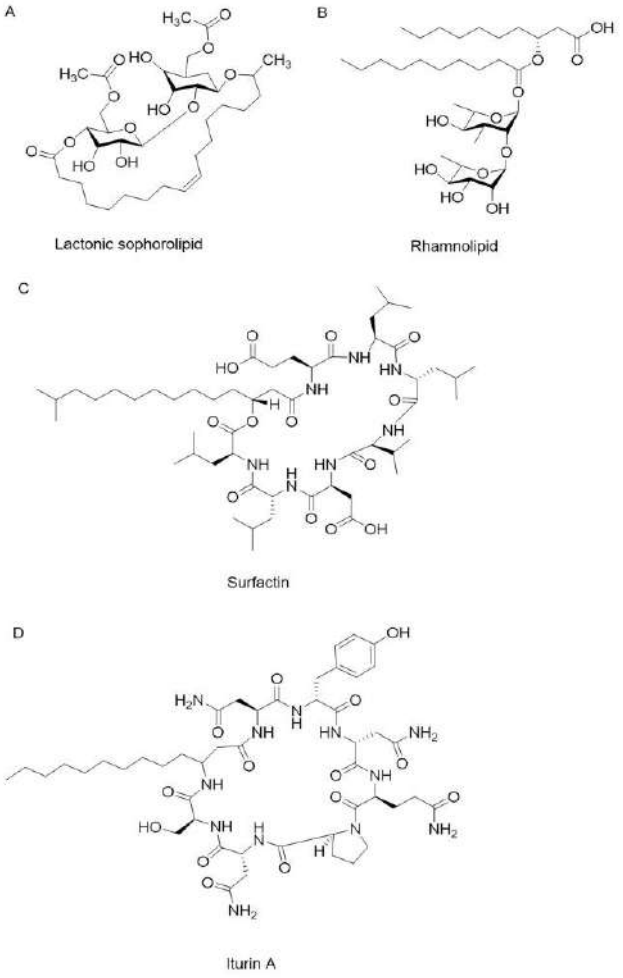

Fig. 4 Chemical structures of biosurfactants produced by SSF. A) Lactonic sophorolipids. B) Rhamnolipid. C) Surfactin. D) Iturin A.
Fig. 4 Estructuras químicas de biosurfactantes producidos por SSF: A) Sofrolípidos lactónicos. B) Ramnolípido. C) Surfactina. D) Iturina A.

3.4 Polymers

Unlike small antimicrobial molecules, polymers offer an effective solution for surface-bound pathogens, particularly when they are biocompatible and sustainable materials for medical applications, such as prostheses and band aids. Furthermore, incorporating antibiotics into polymeric matrices reduces their toxicity, enhances stability, and extends their half-life (Brooks & Brooks, 2014).

Polymers are macromolecules formed from repeating units called monomers. They are an essential class of molecules as they usually support the structural and biological functions of living organisms. In addition to the biological activity studied, many other parameters can be used to characterize a macromolecule, notably its monomeric composition and arrangement, chain length, and morphology.

Moreover, for the same class of molecules, these parameters may have an essential influence on their biological activity (Carboué et al., 2022). A distinction can be made regarding the inherent nature of the antimicrobial properties, although this can also be applied to any biological activity. Indeed, some polymers, such as natural polymers (e.g., chitosan) or synthetic polymers (e.g., polyethyleneimine), exhibit inherent antimicrobial properties. In contrast, some polymers can be chemically functionalized to obtain antimicrobial properties (Jain et al., 2014). It is also possible to functionalize an existing antimicrobial polymer to improve its antimicrobial properties, as in the case where phenolic acid derivatives were grafted onto chitosan (Wang et al., 2019). In the present section, the focus is on the polymers produced by SSF; therefore, only natural polymers with inherent activities were considered.

3.4.1 Carbohydrate polymers

Carbohydrate polymers or polysaccharides are the most prevalent biopolymers on Earth. Among carbohydrate polymers, cellulose is the most abundant, followed by chitin (Shen et al., 2016). A polymer is typically classified as a polysaccharide when it contains at least ten monosaccharide units. Polysaccharides can be classified based on their composition (homo- and heteropolysaccharides), type of glycosidic bonds, and cellular localization, within the cell wall, secreted outside the cell as exopolysaccharides, or retained intracellularly as endopolysaccharides (Osińska-Jaroszuk et al., 2015).

Most fungal exopolysaccharides are produced in SmF from Basidiomycetes and Ascomycetes. Endophytic fungi are an excellent source of exopolysaccharides (Zeng, Yang, Wang, et al., 2019). For instance, two heteropolysaccharides containing arabinose, glucose, mannose, and galactose were produced by *Fusarium solani* grown on a solid medium containing rice, bean dregs, rice bran, and corn bran for 30 days. However, due to the complexity of separating the medium from the mycelium in SSF, it remains unclear whether these compounds are exopolysaccharides or endopolysaccharides. Both molecules showed immunomodulatory activities, and one had interesting antioxidant potential evaluated through a radical scavenging assay. This difference in antioxidant activity was attributed to the difference in sugar composition between heteropolysaccharides. Indeed, a higher content of galactose and glucose resulted in higher antioxidant activity (Zeng, et al., 2019a).

Nonetheless, bacterial exopolysaccharides may also be successfully produced using SSF. For instance, Gram-negative *Bacillus Kosakonia cowanii* was cultivated on sugarcane bagasse and broadbean seed capsules in SSF to produce exopolysaccharides. Considering the cost of the medium and comparing their yield (41.62 mg gds^{-1}) with the yield reported in the literature using SmF and similar conditions (14.88 mg L^{-1}), the authors suggested that 30 % cost saving could be obtained (Gao et al., 2020). SSF media are not limited to lignocellulosic materials; for instance, squid processing byproducts in a mixture with maize cob meal were successfully used as a solid medium to produce exopolysaccharides from *Bacillus licheniformis* during the SSF process (Fang et al., 2013). Xanthan, a heteropolysaccharide of high industrial importance for its use as a texturing agent in food, was

produced from *Xanthomonas campestris* grown on apple pomace, and the yields were comparable to those obtained under SmF conditions (Stredansky & Conti, 1999). Moreover, it is worth mentioning that the presence of oligosaccharides and phenolic compounds generated as degradation products during the enzymatic degradation of lignocellulosic byproducts may also participate in the overall antioxidant potential through inherent ant synergistic actions. Thus, when purification of the crude extract is not required, the use of lignocellulosic byproducts in SSF may offer distinct advantages (Forsan et al., 2025).

Another carbohydrate polymer is chitosan (Fig. 5A), which is an N-deacetylated chitin derivative. This deacetylation process is typically incomplete; therefore, chitosan is a copolymer composed of *N*-acetylglucosamine and glucosamine (Ravi Kumar, 2000). For chitosan, the degree of deacetylation must be greater than 60 %. With a pKa value of 6.3, the amino groups confer solubility to chitosan in mildly acidic aqueous solutions (Hamedi et al., 2018). In such solutions, these functional groups are protonated, giving chitosan its polycationic properties and allowing its absorption onto negative cellular membranes (Raafat et al., 2008). Several models have been proposed to explain the mechanisms underlying the antimicrobial activity of chitosan; for instance, in gram-positive bacteria, the peptidoglycans in the cell wall are hydrolyzed, generating a leakage of the intracellular components and subsequent cellular death.

However, in gram-negative bacteria, chitosan interacts with lipoproteins and lipopolysaccharides from the outer membrane, changing its permeability and blocking the transport of nutrients. Other studies reported the antimicrobial intracellular action of chitosan, which, through crossing the cell membrane, binds to DNA and prevents its transcription (Sahariah & Másson, 2017). Although the antimicrobial activity of chitosan is influenced by its solubility, which is dependent on the degree of deacetylation and solution pH, the role of molecular weight remains unclear and appears to vary across microbial strains (Yilmaz Atay, 2019). Chitosan is traditionally produced by alkali extraction of shells from molluscans and crustaceans. However, fungi also contain this macromolecule in their cell wall. Thus, fungal chitosan can be produced using either SSF or SmF, circumventing the additional steps involved in conventional production, such as decolorization and demineralization (Ghormade et al., 2017). There are examples of the successful production of chitosan using SSF and agroindustrial byproducts such as *Rhizopus oryzae* on soybean meal, corn straw, or potato peel (Suntornsuk et al., 2002; Omogbai & Ikenebomeh, 2013; Kleekayai & Suntornsuk, 2011). The difference in chitosan yields and properties may be observed between SSF and SmF for similar nutritional conditions, but highly depends on the strain and medium used. Nwe et al. (2002), for example, through using *Gongronella butleri*, observed that SmF led to 1.5-fold higher chitosan production compared to the one obtained with SSF – the basis of comparison was the initial carbon source –, although in this case, the chitosan had a lower molecular weight.

3.5 Poly(amino acids)

Poly(amino acids) are biocompatible and biodegradable polymers. A homopoly(amino acid) is composed of one type of amino acid in its backbone. Although a wide variety of amino acids exists, only four homopoly(amino acid)s have been reported in nature to date: poly(γ-glutamic acid), poly(ε-L-lysine), poly(γ-L-diaminobutanoic acid), and poly(L-diaminopropionic acid). In contrast, polymers consisting of more than one type of amino acid are called heteropoly(amino acid)s. For instance, poly(L-arginyl-D-histidine) is produced by the ergot fungus *Verticillium kibiense* (Kurihara et al.,

2008). Poly(amino acid)s have interesting biological activities, primarily attributed to their poly-ionic nature.

ε-Poly-lysine (Fig. 5B) is an oligomer consisting of 25–35 residues of L-lysine connected by unique linkages between ε-amino groups and α-carboxyl groups. It is water-soluble, biodegradable, edible, and non-toxic to humans and the environment (Shih et al., 2006). ε-Poly-lysine, similar to chitosan, is a polycationic compound. Indeed, it has primary amine functions along its backbone and thus displays cationic properties, with an isoelectric point of around pH = 9, facilitating electrostatic interactions with negatively charged cell membranes, ultimately leading to membrane disruption and cell death (Cai et al., 2025). The first study dealing with poly-ε-lysine production through SSF reported a production yield of 86.62 mg gds^{-1} using *Streptomyces albulus* growing on a mixture of rapeseed cake and wheat bran supplemented with glucose and $(NH_4)_2SO_4$ incubated at 30 °C for 8 days (Xu et al., 2017). Notably, a comparable yield (75.51 mg gds^{-1}) was also achieved under composting conditions with 60 kg of the medium. Considering the cost of raw material and using a yield of 25.8 g L^{-1} as a basis of comparison for production carried out in SmF, they concluded that SSF would allow a 32 % reduction in the culture medium.

Some strains can simultaneously produce different homopoly(amino acid)s. A strain of *S. albulus* was grown on spent mushroom residues using SSF to successfully produce ε-poly-lysine and poly(L-diaminopropionic acid) (Fig. 5C) (Kurihara et al., 2008). This co-production is particularly promising for the direct use of crude extracts given the complementary antimicrobial profiles of each compound. For example, compared with ε-poly-lysine, poly(L-diaminopropionic acid) exhibits stronger inhibitory activities against yeasts but weaker activities against bacteria (Xia et al., 2013).

Another noteworthy example is poly-γ-glutamic acid (Fig. 5D), which is extensively produced by *Bacillus* species. It is an anionic homo-polyamide composed of D- and L-glutamic acid monomers linked by an amide linkage between the α-amine and γ-carboxylic acid groups. Although anionic in nature, poly-γ-glutamic acid displays notable antimicrobial activity, particularly against Gram-positive bacteria. Both Gram-negative bacteria and poly-γ-glutamic acid are negatively charged, and antimicrobial activity requires more product concentration. Moreover, this activity may be restricted to ionic interactions and the hydrophobic nature of the molecule that participates in cell adhesion (Ijadi Bajestani et al., 2018). Poly-γ-glutamic acid production was successfully performed using SSF and a mixture of swine manure, soybean cake, and wheat bran as the culture medium (Chen et al., 2005). Fang et al. (2020) used *Bacillus amyloliquefaciens* to produce poly-γ-glutamic acid by SSF on corn stalks and soybean meal. The authors compared sterilized and non-sterilized solid media and reported that although the yield was lower, the fermentation process was faster under non-sterilized conditions. This finding is relevant from a process engineering standpoint, as sterilization steps significantly increase production costs on an industrial scale.

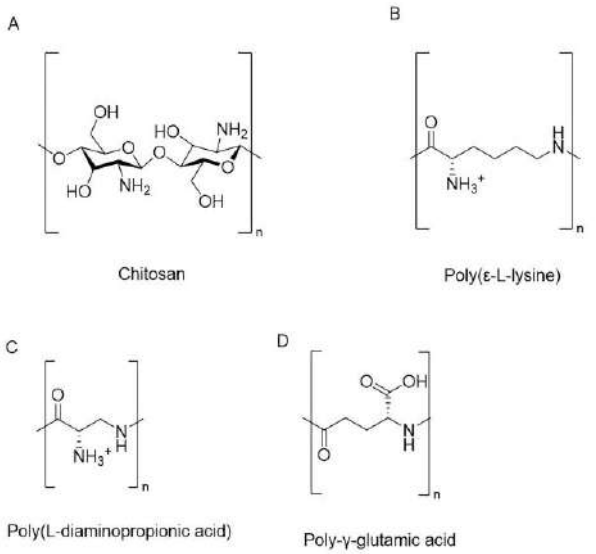

Fig. 5 Chemical structures of polymers produced by SSF. A) Chitosan. B) Poly-ε-lysine. C) Poly(L-diaminopropionic acid). D) poly(γ-glutamic acid).
Fig. 5 Estructuras químicas de polímeros producidos por SSF. A) Quitosano. B) Poli-ε-lisina. C) Poli(ácido L-diaminopropiónico). D) Poli(γ-ácido glutámico).

3.6 Enzymes

Some enzymes with pharmaceutical applications, such as amylases, lipases, and proteases, have been developed under SSF. Amylases belong to a large group of glycosyl hydrolase enzymes that catalyze the breakdown of complex carbohydrates such as starch and dextran. These enzymes are used as diagnostic aids and show potential for diagnostic and therapeutic applications in cancer, infection, wound healing, and drug delivery (Azzopardi et al., 2016). Stable amylases, active over a broad range of pH and temperatures, have been produced from wheat bran as a solid substrate by *Bacillus amyloliquefaciens* KCP2, *Bacillus subtilis* MTCC 121, and *Gongronella butleri* (Raul et al., 2014; Prajapati et al., 2015; Cavalheiro et al., 2017).

Lipases, classified as triacylglycerol acyl hydrolases, are serine hydrolases that hydrolyze the ester bonds of tri-, di-, and mono-glycerides to release fatty acids and glycerol. These enzymes are used to synthesize pharmaceutical intermediates (Ramos Sanchez et al., 2015). For example, a lipase from *Geotrichum candidum* was employed in the stereoselective acetylation of racemic [1- (hydroxy)-4-(3-phenyl) butyl] phosphonic acid diethyl ester to produce a chiral intermediate for the chemical synthesis of an anti-cholesterol drug (Ramos Sanchez et al., 2015). CAL-B lipase was used in a racemic mixture of 2-pentanol to produce a chiral intermediate for the synthesis of anti-Alzheimer drugs synthesis. Lipases from *C. cylindracea* and *C. antartica* were applied to resolve enantiomers of flurbiprofen, naproxen, ibuprofen, suprofen, and baclofen, and to synthesize antiviral drugs such as lobucavir, an antiviral of hepatitis B, and ribavirin (Ramos Sanchez et al., 2015). Lipases are mainly produced by yeasts and filamentous fungi, which often exhibit higher lipase yields in SSF than in SmF (Ramos Sanchez et al., 2015). Lipid-rich substrates, such as coconut oil cake, sesame oil cake, babassu oil cake, olive cake, and palm kernel cake are preferred for lipase production (Ramos Sanchez

et al., 2015; Lopes et al., 2022). *Yarrowia Lipolytica* IMUFRJ50682, for instance, produced lipase with hydrolytic activity under varying temperature and pH conditions in SSF using canola cake and soybean meal (Souza et al., 2017). Similarly, rice bran and Jatropha seed cake were used for lipase production by *Aspergillus niger* (Putri et al., 2020).

Proteases catalyze the hydrolysis of peptide bonds, breaking down proteins into smaller peptides or amino acids (Steudler et al., 2019). Microbial alkaline serine proteases have notable pharmaceutical relevance. Immobilized subtilisins have been incorporated into formulations for the treatment of burns and wounds. Several protease therapies are currently under clinical investigation, owing to their collagenase activity. Alkaline proteases have been used to treat conditions such as Dupuytren's disease, Peyronie's disease, glaucoma, intervertebral disc herniation, debridement, keloids, vitrectomy, and cellulite. Additionally, they are used in therapies for thrombolysis (urokinase, fibrinolytic enzymes), hemophilia (factor VIIa), sepsis (activated protein C), muscle spasms (botulinum toxin A and B), lymphocytic leukemia (asparaginase), purulent wounds, and abscesses (elastoterase) (Matkawala et al., 2021). *Neurospora crassa* CGMCC3088 produced proteases via SSF using okara as a substrate, showing extended stability in organic solvents, which is promising for bioactive ingredient formulation (Zheng et al., 2020). Other commonly used solid substrates include wheat straw, sugarcane bagasse, rice straw, and rice husks (Steudler et al., 2019).

Additionally, peptides with antioxidant activities can be produced using agro-industrial residues and SSF. Bioactive peptides, derived from the hydrolysis of inactive parental proteins, have been shown to reduce blood pressure and address complications associated with diabetes and cancer while also exhibiting antioxidant properties (Manfredini et al., 2021). For instance, antioxidant peptides were generated from grapeseed meal fermented by *Bacillus subtilis* 10160, with concentration-dependent-activity (He et al., 2012). In another example, fermentation of soybean meal by *B. amyloliquefaciens*, *Lactobacillus sp*., and *Saccharomyces cerevisiae* led to the elimination of trypsin inhibitors, synthesis of proteases and small peptides, and an increase in phenolic compounds, ultimately enhancing antioxidant activity (Manfredini et al., 2021).

3.7 Vitamins

Vitamins are organic compounds that are essential for the normal functioning of the body because of their biochemical and biological roles. Since the body cannot synthesize some vitamins, they must be obtained from the diet, with plants serving as their primary sources (Ball, 2004). Water-soluble vitamins, such as riboflavin, nicotinic acid, nicotinamide, and vitamin B6 (Fig. 6A, B, C, D), were produced through SSF of tempeh using *Rhizopus oligosporus*, *R. arrhizus*, and *R. stolonifer*. Vitamin B12 (Fig. 6E) was synthesized when *Citrobacter freundii* and *Klebsiella* were added to the SSF process (Pandey et al., 2000), highlighting the importance of microbial synergism. Furthermore, *Rhizopus oligosporus* independently fermented both raw and roasted buckwheat groats, resulting from 1.5 to 3-fold increase in the concentrations of thiamine (B1), pyridoxin (B6), and L-ascorbic acid (Fig. 6F, 6H) (Wronkowska et al., 2015). Similarly, *Saccharomyces cerevisiae*, *Candida utilis*, and *Torula utilis* enhanced vitamin C production from apple pomace powder (Joshi & Sandhu, 1996), whereas *Lactobacillus* casei improved the vitamin B1 and B2 content of soybean flour (Li et al., 2020).

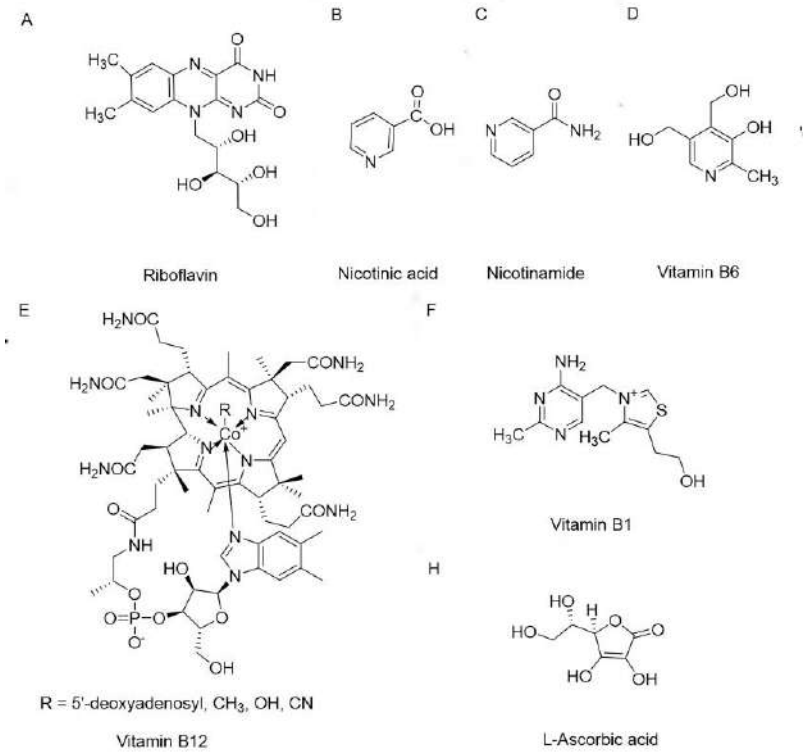

Fig. 6 Chemical structures of vitamins produced by SSF. A) Riboflavin. B) Nicotinic acid. C) Nicotinamide. D) Vitamin B6. E) Vitamin B12. F) Vitamin B1. H) L-Ascorbic acid.
Fig. 6 Estructuras químicas de vitaminas producidas por SSF. A) Riboflavina. B) Ácido nicotínico. C) Nicotinamida. D) Vitamina B6. E) Vitamina B12. F) Vitamina B1. H) Ácido L-ascórbico.

3.8 Miscellaneous

Some secondary metabolites in pharmaceutical products, such as carotenoids, lovastatin, and cordycepin, show great promise owing to their therapeutic properties. Carotenoids, such as lycopene, exhibit potent antioxidant activity and have been associated with improvements in cardiovascular diseases, inflammatory events, oxidative stress-mediated dysfunction, and cancer resistance. Lycopene was extracted through SSF of tomatoe waste using *Aspergillus niger* GH1. It was found that total carotenoid recovery was below 70 % at moisture, highlighting the importance of this parameter in the bioprocess (Mendez-Carmona et al., 2022). Lovastatin (Fig. 7A), a widely used hypercholesterolemic drug, was efficiently produced via SSF of wheat bran by *Aspergillus terreus* ATCC 10020, reaching a yield of 8.67 mg gds^{-1}. In this way, lovastatin significantly reduced insulin levels, body mass, LDL-C, triglycerides, blood glucose, and thiobarbituric acid-reactive substances in mice fed a high-fat diet (Al-Saman et al., 2021). Cordycepin (Fig. 7B), a nucleoside derivative synthesized by *Cordyceps militaris*, is commonly used as a functional food and medicine in Southeast Asia to treat and prevent obesity. It also exhibits anticancer, antiviral, antileukemic, and hypolipidemic activities. SSF using brown rice has emerged as a promising method for cordycepin production, as it is more difficult and costly to purify through chemical synthesis than through biological pathways (Wen et al., 2014).

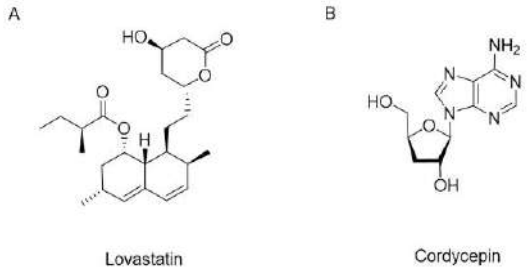

Fig. 7 Chemical structures of miscellaneous secondary metabolites produced by SSF. A) Lovastatin. B) Cordycepin.
Fig. 7 Estructuras químicas de metabolitos secundarios diversos producidos por SSF. A) Lovastatina. B) Cordicepina.

Table 2. Microorganisms and residues used to produce bioactive compounds by Solid-state fermentation.
Tabla 2. Microorganismos y residuos utilizados en la producción de compuestos bioactivos mediante fermentación en estado sólido.

Compound	Bioactive compound	Microorganism	Solid residue / substrate	Reference
Antibiotics	Cephalosporin C	*Acremonium chrysogenum*	Sugarcane bagasse	Tabaraie et al., 2012
	Rifamycin B	*Amycolatopsis mediterranei*	Nut shells, coconut oil cake	Vastrad & Neelagund, 2012
	Paromomycin	*Streptomyces rimosus*	Corn bran	El-Housseiny et al., 2021
Aroma compounds	Vanillin	*Enterobacter hormaechei*	Sugarcane bagasse, fruit peels	Mehmood et al., 2022
	2-Phenylethanol	*Pichia kudriavzevii*	Apple pomace, sugarcane bagasse	Martínez-Ávila et al., 2020
Biosurfactants	Sophorolipids	*Candida bombicola*	Sunflower oil cake + soybean oil	Rashad et al., 2014
	Rhamnolipids	*Pseudomonas aeruginosa*	Sugarcane bagasse + corn bran	Camilios-Neto et al., 2011
	Surfactin	*Bacillus subtilis*	Millet, peanut oil cake	Ghribi et al., 2012
Polymers	Chitosan	*Rhizopus oryzae*	Potato peel	Kleekayai & Suntornsuk, 2011
	ε-Poly-L-lysine	*Streptomyces albulus*	Rapeseed cake + wheat bran	Xu et al., 2017
Enzymes	Amylases	*Bacillus amyloliquefaciens*	Wheat bran	Prajapati et al., 2015
	Lipases	*Yarrowia lipolytica*	Canola cake, soybean meal	Souza et al., 2017
Others	Riboflavin, niacin	*Rhizopus oligosporus*	Soybeans (tempeh)	Pandey et al., 2000
	Lovastatin	*Aspergillus terreus*	Wheat bran	Al-Saman et al., 2021
	Cordycepin	*Cordyceps militaris*	Brown rice	Wen et al., 2014

4. Future perspectives of Solid-state fermentation

Although solid-state fermentation (SSF) offers significant advantages to produce bioactive compounds with pharmaceutical potential, several technical and regulatory limitations still constrain its large-scale implementation. The inherent heterogeneity of SSF systems complicates accurate process monitoring and control, particularly for critical parameters such as temperature, moisture content, pH, and oxygen availability. The integration of advanced sensing technologies, predictive modeling, and data-driven control strategies represents a promising pathway to improve process robustness, reproducibility, and scalability.

In addition, the variability of solid substrates, together with the absence of dedicated regulatory frameworks for SSF-based pharmaceutical processes, remains a major barrier to industrial adoption. Future progress will rely on substrate standardization, microbial strain improvement, bioreactor desing, and the establishment of clear regulatory guidelines, enabling SSF to evolve from a predominantly laboratory-scale approach into a reliable, scalable, and sustainable platform for pharmaceutical bioprocesses.

5. Conclusion

Pharmaceutical products that contain microbial bioactive compounds play a vital role in promoting human health and represent promising alternatives to synthetic drugs and health care products, offering greater selectivity, reduced toxicity, and fewer side effects. Therefore, the development of novel fermentation strategies to enhance production is important. SSF is a sustainable and cost-effective approach for the pharmaceutical industry, offering high product yields while utilizing low-cost substrates and minimizing environmental impact. Pharmaceutical products typically require high purity, and SSF often uses agro-industrial byproducts. Therefore, the resulting crude extracts tend to be complex and may require extensive downstream processing to meet purity standards. These additional purification steps can significantly increase the overall production costs. Finally, most current studies on SSF for bioactive compound production are limited to lab-scale bioreactors. Therefore, further studies are necessary to address the challenges related to the process scale-up and control. By addressing current limitations and showcasing innovative applications, solid-state fermentation is positioned as a viable complementary strategy for pharmaceutical bioprocesses.

Author contributions

L. M. V. V.: Conceptualización, redacción-revisión y edición. Q. C.: Conceptualización, redacción-revisión. S. H. O.: Supervisión, redacción – revisión. E. F. T.: Supervisión, redacción – revisión y edición. I. N. C. S.: Conceptualización, redacción-revisión y edición.

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Conflict of interest

The authors declare that they have no conflict of interest.

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