Secondary Metabolism's Main Biosynthetic Pathways in Solid-State Fermentation

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Microbial secondary metabolites are low-molecular-weight compounds synthesized by microorganisms after the growth phase. Secondary metabolites are not directly involved in microbial growth. Solid-state fermentation (SSF) is a process whereby microorganisms grow in the absence of free water or with low water content. It has been used since ancient times to obtain fermented foods such as koji, bread, and cheeses.

agro-industrial residue | microbial secondary metabolite | biotransformation

1. Introduction

Microbial secondary metabolites are low-molecular-weight compounds synthesized by microorganisms after the growth phase. Secondary metabolites are not directly involved in microbial growth. Still, they play a significant role in competition, antagonism, and self-defense mechanisms [1]. These compounds have a variety of chemical structures, and many have biological activities such as antimicrobial, antiviral, antioxidant, antitumor, vasodilator, vasoconstrictor, diuretic, and laxative activities, among others [2]. Utilizing microbial cultures for secondary metabolite production has proven to be an effective strategy for reducing production costs and carbon footprints. Moreover, microbial production also contributes to preserving plant biodiversity [3] since microorganisms can produce some plant secondary metabolites through the biotransformation of precursors. Microbial production then allows humans to avoid the disadvantages of plant extraction, like low yield, which leads to plant over-exploitation.

Production of microbial secondary metabolites is influenced by diverse culture conditions such as the composition of culture media, the carbon/nitrogen ratio, salinity, the presence of metal ions, temperature, pH, and oxygen concentration [4]. The fermentation system significantly influences the production of secondary metabolites. They are mainly produced by submerged fermentation (SmF) due to the ease of measuring, monitoring, and controlling process variables. Nonetheless, solid-state fermentation (SSF) is recognized to imitate the natural environment for the growth of microorganisms, representing an advantage for obtaining some metabolites [5].

SSF is a process whereby microorganisms grow in the absence of free water or with low water content [6]. It has been used since ancient times to obtain fermented foods such as koji, bread, and cheeses. Even in the last century, SSF has produced compounds for the food, pharmaceutical, textile, biochemical, and energy industries [7]. This innovative culture system has produced a wide range of secondary metabolites, including bioactive compounds, enzymes, polyphenols, food additives, and others [8][9][10].

There are two types of SSF. The first is the most common and uses a natural solid material acting as substrate and support. The second uses an inert support impregnated with a nutritive culture medium. In both systems, advantages of SSF over SmF have been reported, such as higher yield in the production of enzymes and secondary metabolites. Furthermore, some microorganisms only produce certain enzymes or secondary metabolites in SSF, even though they can grow well in SmF [11]. Therefore, different authors have used SSF to produce pigments, antibiotics, statins, biosurfactants, phenolic compounds, and other secondary metabolites. **Table 1** shows some examples of secondary metabolites that SSF can obtain.

Table 1. Examples of secondary metabolites produced by SSF.

Metabolite and Its Potential Application	Microorganism	Solid Support	Yield (mg/g SS)	Reference
Pigments				
Monascin, ankaflavin, rubropunctatin, monascorubrin, rubropunctamin, monascorubramine, etc.	*Monascus* sp.	Rice	49.65 *	[12][13]
Antibiotics				
Penicillin	*Penicillium chrysogenum*	Sugarcane bagasse	7–8	[14][15]
Cephalosporin C	*Acremonium chrysogenum*	Sugarcane bagasse	3.2	[16][17]
Paromomycin	*Streptomyces rimosus*	Corn bran	2.2	[18]
Neomycin	*Streptomyces fradiae*	Nylon sponge	n.d.	[19]
Rifamycin B	*Nocardia mediterranei*	Sunflower oil cake	9.87	[20]
Antifungal				
Sclerotiorin	*Penicillium sclerotiorum*	Rice	n.d.	[21]
Griseofulvin	*Penicillium griseofulvum*	Rice bran	9–10	[22]
Natamycin	*Streptomyces gilvosporeus*	Wheat bran, rapeseed cake, and rice hull	9.62	[23]
Statins				

Metabolite and Its Potential Application	Microorganism	Solid Support	Yield (mg/g SS)	Reference
Lovastatin	*Aspergillus terreus*	Glucose and lactose	19.95–25	[24][25][26]
Compactin (mevastatin)	*Penicillium brevicompactum*	Soybean meal	1.406	[27]
Monacolin K	*Monascus ruber*	Millet	19.81	[28]
		Rice and bran	14.53	[29]
Biosurfactants				
Surfactin	*Bacillus subtilis*	Olive cake flour	30.67	[30]
	Bacillus amyloliquefaciens	Soybean flour	15.03	[31]
Iturin	*Bacillus subtilis*	Defatted soybean meal, wheat bran and ricehusk	5.58	[32]
Rhamnolipids	*Pseudomonas aeruginosa*	Polyurethane foam	39.8 **	[33]
		Soybean meal	19.68	[34]
Sophorolipids	*Starmerella bombicola*	Polyurethane foam	211 ***	[35]
		Wheat straw	195	[36]
Phenolics				
Vainillin	*Enterobacter hormaechei*	Sugarcane bagasse	4.76	[37]
	Enterobacter hormaechei	Pomegranate peels	0.462	[38]
	Streptomyces sannanensis	Wheat straw	2.74	[39]
Gallic acid	*Aspergillus niger*	Black plum seed	14.5	[40]
Hispidin	*Phellinus linteus*	Brown rice and pearl barley	0.375	[41]
Immunosuppressants				
Mycophenolic acid	*Penicillium brevicompactum*	Parmal rice	4.5	[42]

Metabolite and Its Potential Application	Microorganism	Solid Support	Yield (mg/g SS)	Reference
Cyclosporin A	*Tolypocladium inflatum*	Wheat bran flour and coconut oil cake [46]	6.48	[43]
Phytohormones				
Gibberellic acid	*Gibberella fujikuroi*	Amberlite IRA-900	n.d.	[44]
Alkaloids				
Ergotamine	*Claviceps purpurea*	Rice	≈0.015	[45]

* Optical density unit (ODU)/g SS, ** g/L, *** mg/g substrate, n.d. = not determined.

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microorganisms affecting cellular processes such as DNA replication, transcription, cell wall synthesis, and cell membrane disruption [47]. Antibiotics are produced commercially by SmF. However, SSF is an alternative system with advantages for large-scale production, such as higher yields in shorter periods [11]. For this reason, various authors have investigated the production of antibiotics such as penicillin [14][15], cephalosporin C [16][17], paramomycin [18], neomycin [19], and rifamycin [20] by SSF.

On the other hand, statins are a group of drugs that lower blood cholesterol levels, decreasing the risk of heart attack or stroke. Filamentous fungi produce natural statins (lovastatin, compactin, and monacolin K). Notably, the industrial production of lovastatin is mainly carried out by SmF using *Aspergillus terreus* [48]. However, several authors have described the advantages of SSF for lovastatin production compared to SmF. For example, Baños et al. [24] reported 30 times higher lovastatin production by *A. terreus* TUB F-514 in SSF than in SmF. In addition, the specific production was 14 times higher in SSF. Therefore, the Indian biotech company Biocon Ltd. developed a method to produce lovastatin in SSF using the Plafractor bioreactor [49]. Lovastatin produced by SSF received FDA approval for sale in the United States in 2001.

Other molecules produced at the end of the exponential growth phase of certain bacteria, yeasts, and molds are biosurfactants, which reduce surface and interfacial tension due to their amphiphilic nature. These molecules are involved in cell development, biofilm formation, osmotic pressure regulation, and hydrophobic substance assimilation [50]. They are produced by certain microorganisms, mainly by SmF. Still, during their manufacture, a large amount of foam is produced, increasing the risk of contamination and reducing productivity. Conversely, SSF eliminates the foaming problem and reduces energy and water consumption during production [34]. For this reason, different researchers have investigated SSF to produce biosurfactants such as sophorolipids [35][36], rhamnolipids [33][34], surfactin [30][31], and iturin [32], among others.

Some secondary metabolites obtained from plants cannot be produced directly by microorganisms. However, some microorganisms can biotransform the chemical precursors of those plants' secondary metabolites. For example, vanillin is an essential flavoring agent in the food industry, traditionally extracted from vanilla pods. Several bacteria of the genera *Amycolatopsis*, *Streptomyces*, *Pseudomonas*, *Delftia*, and *Enterobacter* can catalyze the conversion of ferulic acid to vanillin. Some authors have investigated the use of ferulic acid-rich agro-industrial by-products such as sugarcane bagasse [37], pomegranate peels [38], and wheat straw [39] to produce biovanillin through SSF.

2. Main Biosynthetic Pathways of Secondary Metabolism

Secondary metabolites are not essential for organisms' growth, development, reproduction, or energy production. Therefore, these compounds are not produced by all microbial species. Secondary metabolites are synthesized from primary metabolites, such as acetyl-coenzyme A and amino acids, through secondary metabolic pathways [51].

Two metabolic pathways synthesize the precursors of phenolic compounds: the shikimic acid and malonic acid pathways. The shikimic acid pathway is most important in plants. The malonic acid pathway is an essential source of phenolics in fungi and bacteria but is less significant in plants [52]. Terpenoid precursors can be synthesized by two metabolic pathways: the mevalonic acid pathway or the methylerythritol phosphate pathway. The mevalonic acid pathway is present in plants, animals, yeast, fungi, archaea, and some eubacteria. The methylerythritol phosphate pathway is present in most bacteria, cyanobacteria, and plant plastids [53]. Primary and secondary metabolic pathways are interrelated, as shown in **Figure 1**. The regulation of secondary metabolism is a complex process. Therefore, in order to improve the production of secondary metabolites by microorganisms, it is essential to understand the metabolic pathways involved. The main metabolic pathways related to the production of secondary metabolites in microorganisms are described below.

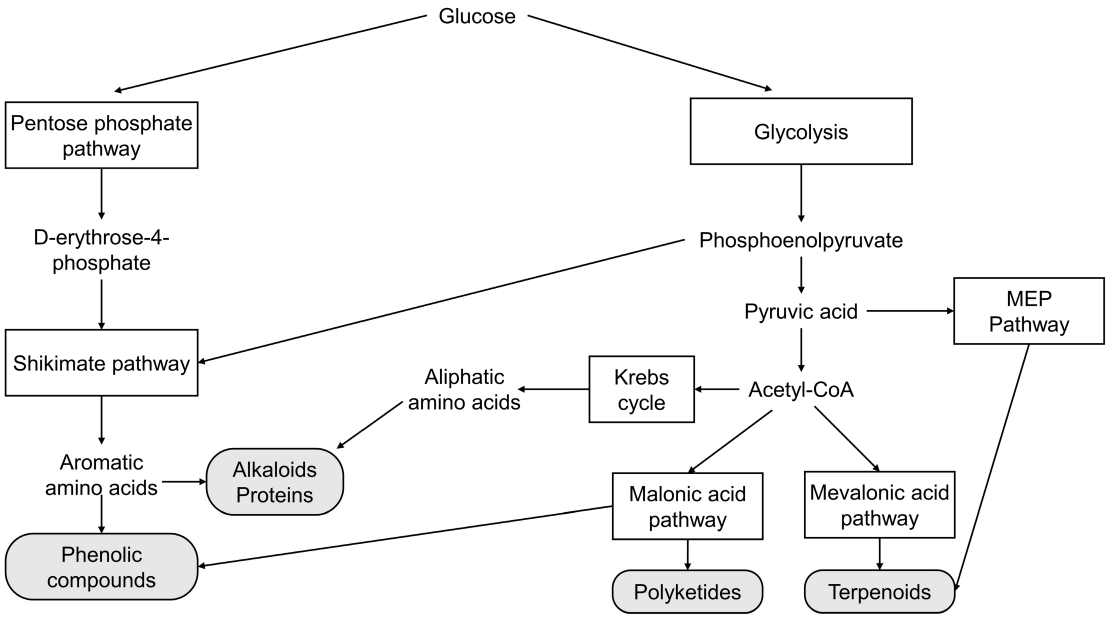

Figure 1. Schematic diagram of the main metabolic pathways involved in the production of secondary metabolites by microorganisms.

2.1. Shikimate Pathway

The shikimate pathway provides precursors for aromatic molecules in bacteria, fungi, and plants but not in animals. This pathway provides the aromatic amino acids (L-phenylalanine, L-tyrosine, and L-tryptophan) necessary for protein synthesis. Aromatic amino acids also serve as precursors for secondary metabolites, such as phenolic compounds and some alkaloids [54].

The shikimate pathway consists of seven enzymatic reactions: First, phosphoenolpyruvate (an intermediate metabolite in the Embden–Meyerhof–Parnas pathway) and D-erythrose-4-phosphate (an intermediate metabolite in the pentose phosphate pathway) are converted to 3-deoxy-D-arabino-heptulosonate-7-phosphate (DAHP) by DAHP synthase. DAHP is then converted to shikimic acid by 3-dehydroquinate (DHQ) synthase, DHQ dehydratase, and shikimate dehydrogenase. Last, shikimic acid is converted to chorismic acid by shikimate kinase, 5-enolpyruvylshikimate 3-phosphate synthase, and chorismic acid synthase. The final product of the shikimate pathway (chorismic acid) can be further transformed into aromatic amino acids by a single reaction. [55]. The phenylpropanoid pathway transforms L-tyrosine and L-phenylalanine into various phenolic compounds in higher plants. No evidence exists of complete phenylpropanoid metabolism in organisms other than land plants. However, some homologous enzymes of this pathway have been found in some bacteria and fungi [56].

The shikimate pathway has different metabolic branches in different microorganisms that lead to the formation of diverse secondary metabolites, such as shikimic acid, gallic acid pyrogallol, chlorogenic acid, and catechol [57]. For example, shikimic acid is an intermediate compound of this pathway. It has a highly functionalized, six-carbon ring with three chiral carbons and a carboxylic acid functional group. Therefore, it is widely used to synthesize valuable products such as the antiviral drug oseltamivir (Tamiflu®) [58].

2.2. Malonic Acid Pathway

Most of the phenolic compounds in higher plants are produced by the shikimate pathway, whereas in bacteria and fungi, the phenolic compounds are also synthesized by the malonic acid pathway [59].

The key enzyme tyrosine ammonia lyase deaminates tyrosine into p-coumaric acid in the malonic acid pathway. It is functionalized into p-coumaroyl-CoA by 4-coumaroyl CoA ligase. Then it reacts with three molecules of malonyl-CoA to give chalcone by chalcone synthase. The obtained tetraoxychalcone is transformed into flavanone–naringenin, which serves as a precursor to other flavonoids [60].

2.3. Mevalonic Acid Pathway (MVA)

The MVA pathway is present in most eukaryotes, archaea, and some bacteria. This pathway begins with the condensation of two acetyl-CoA molecules. It ends with the formation of isopentenyl-pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), the precursors to terpenoid biosynthesis [61].

In the MVA pathway, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) is produced from the sequential condensation of three molecules of acetyl-CoA catalyzed by acetoacetyl-CoA thiolase, and HMG-CoA synthase HMG-CoA is then converted to mevalonic acid by HMG-CoA reductase (HMGCR). Mevalonic acid is sequentially phosphorylated to 5-phosphomevalonate and 5-diphosphomevalonate and decarboxylated to generate IPP by the enzymes mevalonate kinase, 5-phosphomevalonate kinase, and 5-diphosphomevalonate decarboxylase. Finally, DMAPP is produced from IPP by a reversible reaction catalyzed by IPP/DMAPP isomerase [62].

HMGCR is the rate-limiting enzyme in the MVA pathway. There are two classes of HMGCR. Class I includes proteins of eukaryotic origin that are associated with the endoplasmic reticulum and are potentially inhibited by statins. Class II proteins of bacterial origin have low homology with class I HMGCRs (<20%). However, there is considerable similarity between the active sites of both classes of enzymes [63].

2.4. Methylerythritol-Phosphate (MEP) Pathway

The MEP pathway is an alternative route to MVA to produce terpenoid precursors (IPP and DMAPP). Most bacteria, cyanobacteria, and green algae exclusively use the MEP pathway. At the same time, plastid-bearing organisms have both pathways compartmentalized in the cytosol (MVA) and plastids (MEP) [64].

The MEP pathway initiates with the condensation between D-glyceraldehyde 3-phosphate and pyruvate to produce 1-deoxy-D-xylulose 5-phosphate (DXP), catalyzed by DXP synthase. DXP is then reductively isomerized to methylerythritol phosphate (MEP) by DXP reductoisomerase. Coupling between MEP and CTP is catalyzed by CDP-ME synthetase to produce methylerythritol cytidyl diphosphate (CDP-ME). CDP-ME is then phosphorylated to 4-diphosphocytidyl-2-C-methyl-D-erythritol-2-phosphate (CDP-MEP). CDP-MEP is cyclized to 2-C-methyl-D-erythritol-2,4-cyclodiphosphate (MEcPP). The opening of the cyclic pyrophosphate and the C3-reductive dehydration of MEcPP is catalyzed by 2-C-methyl-D-erythritol-2,4-cyclodiphosphate reductase to yield 4-hydroxy-3-methyl-butenyl 1-diphosphate (HMBPP). Finally, HMBPP is reduced to IPP and DMAPP by 4-hydroxyl-3-methyl-butenyl 1-diphosphate reductase [65].

Finally, it should be emphasized that although common molecular patterns and principles underlie life's diverse forms, many differences in primary biosynthetic pathways exist. Many biosynthetic pathways are specific to certain groups of organisms. For instance, pheammonium lyase is a ubiquitous enzyme in fungi that catalyzes the deamination of L-Phe to trans-cinnamic acid. Conversely, only a few cinnamic and benzoic acid-derived metabolites have been described in prokaryotes [66].

From a practical perspective, the choice between using fungi or bacteria depends on the specific metabolite to be produced. Particular fungal or bacterial species exclusively synthesize some metabolites. Vancomycin, a glycopeptide antibiotic class, is produced by *Amycolatopsis* (formerly *Streptomyces*) species, such as A. orientalis or A. keratiniphila [67][68]. Although vancomycin is effective against methicillin-resistant *Staphylococcus aureus* infections [68], the emergence of vancomycin-resistant *S. aureus* has prompted the development of second-generation glycopeptide antibiotics. An example is the recently FDA-approved compound oritavancin. Although semi-synthetic, its production still relies on the in vivo production of vancomycin by *Amycolatopsis* species, and then the chassis is modified by incorporating a 4-(4-chlorophenyl) benzyl group through reductive alkylation [68].

Similarly, some secondary metabolites are exclusively synthesized by fungi. Beauvericin belongs to the cyclic hexadepsipeptide family and is produced via a non-ribosomal pathway utilizing beauvericin synthetase. It sequentially binds hydroxy isovaleric acid and N-methyl-phenylalanine molecules [69]. Certain entomopathogenic fungi generate Beauvericin, which exhibits diverse biological activities, including insecticidal, antimicrobial, and

antitumor properties. Due to the intricate nature of its chemical synthesis, beauvericin production is predominantly accomplished via in vivo biosynthesis using specialized producer strains. Recently, Vásquez-Bonilla et al. [69] reported an enhancement in beauvericin production using solid-state cultures of *Fusarium oxysporum* AB2 compared to liquid cultures, increasing the yield from 0.8 mg/L to 65.3 mg/L. Moreover, they further improved yields by employing mixed cultures of *F. oxysporum* AB2 and *Epicoccum nigrum* TORT, producing 84.6 mg/L.

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