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Chapter 1

An Introductory Chapter: Secondary Metabolites

Durairaj Thirumurugan, Alagappan Cholarajan,
Suresh S.S. Raja and Ramasamy Vijayakumar

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1. Introduction

The metabolism can be defined as the sum of all the biochemical reactions carried out by an organism. Metabolites are the intermediates and products of metabolism and are usually restricted to small molecules. The term "secondary" introduced by A. Kossel in 1891 implies that while primary metabolites are present in every living cell capable of dividing, the secondary metabolites are present only incidentally and are not of paramount significance for organism's life. Though secondary metabolites are derived from primary metabolism, they do not make up basic molecular skeleton of the organism. Its absence does not immediately curtail the life of an organism, a feature contrary to primary metabolite, but survival of the organism is impaired to a larger extent. Its presence and synthesis are observed in ecologically disadvantaged species within a phylogenetic group [1].

The difference between primary and secondary metabolite is ambiguous since many of the intermediates in primary metabolism is overlapping with the intermediates of secondary metabolites [2]. Amino acids though considered a product of primary metabolite are definitely secondary metabolite too. Contrary to the observation that sterols are secondary metabolites that are indispensable part of many structural framework of a cell. The mosaic nature of an intermediate indicates common biochemical pathway being shared by primary and secondary metabolism [3]. The secondary metabolites serve as a buffering zone into which excess C and N can be shunted into to form inactive part of primary metabolism. The stored C and N can revert back to primary metabolite by the metabolic disintegration of secondary metabolite when on demand. There is dynamism and a delicate balance between the activities of the primary and secondary metabolism (**Figure 1**) being influenced by growth, tissue differentiation and development of the cell or body, and also external pressures [4].

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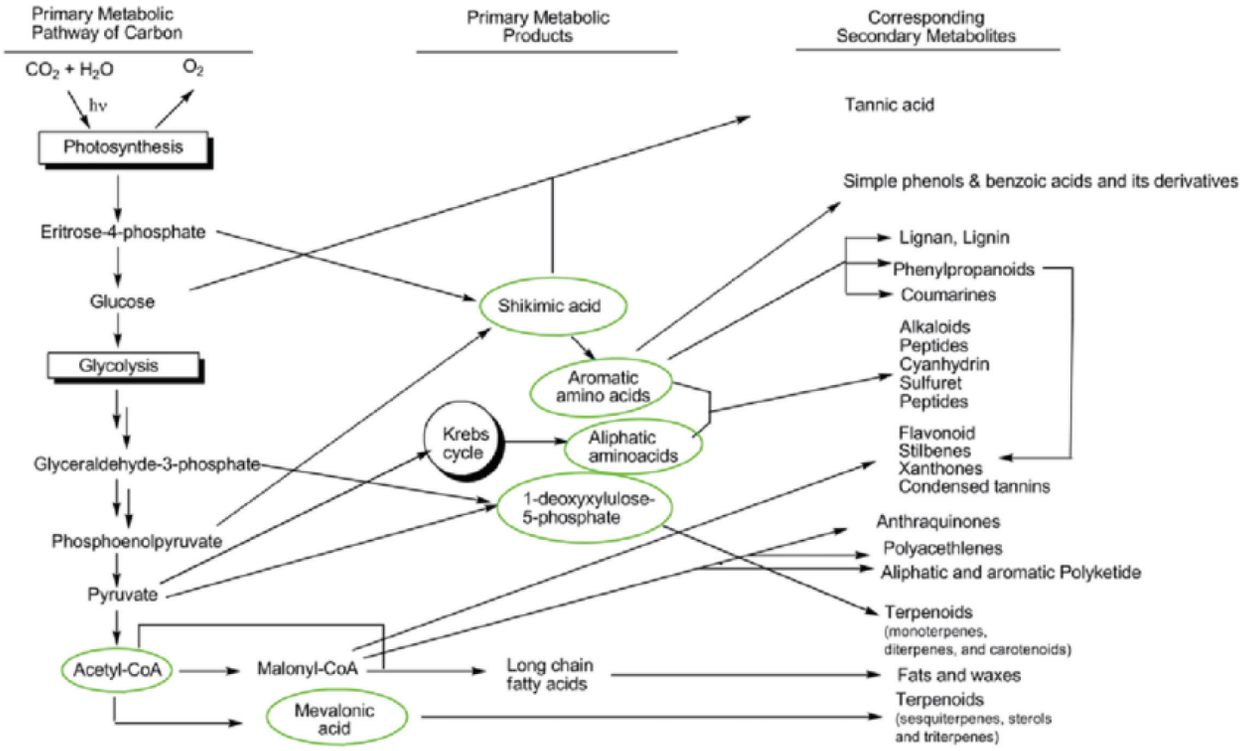


Figure 1. Schematic diagram representing integration of primary and secondary metabolism.

Hence, secondary metabolites or natural products can be defined as a heterogeneous group of natural metabolic products that are not essential for vegetative growth of the producing organisms, but they are considered differentiation compounds conferring adaptive roles, for example, by functioning as defense compounds or signaling molecules in ecological interactions, symbiosis, metal transport, competition, and so on [5]. The multitude of secondary metabolite secretions is harvested by human kind to improve their health (antibiotics, enzyme inhibitors, immunomodulators, antitumor agents, and growth promoters of animals and plants), widen the pyramid of healthy nutrition (pigments and nutraceuticals), enhancing agricultural productivity (pesticides, insecticides, effectors of ecological competition and symbiosis and pheromones), and hence impacting economics our society in a certain positive way. They are a source of antibiotics.

2. Classification of secondary metabolites

Over 2,140,000 secondary metabolites are known and are commonly classified according to their vast diversity in structure, function, and biosynthesis. There are five main classes of secondary metabolites such as terpenoids and steroids, fatty acid-derived substances and polyketides, alkaloids, nonribosomal polypeptides, and enzyme cofactors [6].

2.1. Terpenoids and steroids

They are major group of substances derived biosynthetically from isopentenyl diphosphate. Currently, over 35,000 known terpenoid and steroid compounds are identified. Terpenoids

have different variety of unrelated structures, while steroids have a common tetracyclic carbon skeleton and are modified terpenoids that are biosynthesized from the triterpene lanosterol.

2.2. Alkaloids

There are over 12,000 known compounds of alkaloids, and their basic structures consist of basic amine group and are derived biosynthetically from amino acids.

2.3. Fatty acid-derived substances and polyketides

Around 10,000 compounds are identified and are biosynthesized from simple acyl precursors such as propionyl CoA, acetyl CoA, and methylmalonyl CoA.

2.4. Nonribosomal polypeptides

These amino acids derived compounds are biologically synthesized by a multifunctional enzyme complex without direct RNA transcription.

2.5. Enzyme cofactors

Enzyme cofactors are nonprotein, low-molecular enzyme component [6].

3. Functions of secondary metabolites

The major functions of the secondary metabolites including antibiotics are:

(i) competitive weapons against other livings such as animals, plants, insects, and microorganisms

(ii) metal transporting agents

(iii) agents for symbiotic relation with other organisms

(iv) reproductive agent and

(v) differentiation effectors

(vi) agents of communication between organisms

The other functions include interference in spore formation (not obligatory) and germination [5]. Predominantly, the secondary metabolites are used for variety of biological activities like antimicrobial and antiparasitic agents, enzyme inhibitors and antitumor agent, immunosuppressive agents, etc. [7].

4. Sources of secondary metabolites

The major sources of secondary metabolites are plants (80% of secondary metabolite), bacteria, fungi, and many marine organisms (sponges, tunicates, corals, and snails) (**Table 1**) [8].

Source	All known compounds	Bioactives	Antibiotics
Natural products	Over one million	200,000–250,000	25,000–30,000
Plant kingdom	600,000–700,000	150,000–200,000	~25,000
Microbes	Over 50,000	22,000–23,000	~17,000
Algae, lichens	3000–5000	1500–2000	~1000
Higher plants	500,000–600,000	~100,000	10,000–12,000
Animal kingdom	300,000–400,000	50,000–100,000	~5000
Protozoa	Several hundreds	100–200	~50
Invertebrates	~100,000	NA	~500
Marine animals	20,000–25,000	7000–8000	3000–4000
Insects/ worms/ *etc.*	8000–10,000	800–1000	150–200
Vertebrates (mammals, fishes, amphibians, *etc.*)	200,000–250,000	50,000–70,000	~1000

NA – Data Not Available.
Source: Bérdy [8].

Table 1. Approximate number of known natural metabolites.

4.1. Secondary metabolites of plants

Plant secondary metabolites represent highly economically valuable products. These are used as high value chemicals such as drugs, flavors, fragrances, insecticides, dyes, etc. Plants are rich in a wide variety of secondary metabolites, such as tannins, terpenoids, alkaloids, and flavonoids, which have been found to have *in vitro* antimicrobial properties. Plants have an almost limitless ability to synthesize aromatic substances, most of which are phenols or their oxygen-substituted derivatives [9]. About 25,000 terpenoids are known as secondary compounds and are derived from the five-carbon precursor isopentenyl diphosphate (IPP). In total, around 12,000 known alkaloids are identified, and they possess one or more nitrogen atoms which are biosynthesized from amino acids. The 8000 known phenolic compounds are synthesized either through the shikimic acid pathway or through the malonate/acetate pathway [10].

Many alkaloids are used in medicine, usually in the form of salts. Some examples include vinblastine which has antitumor properties [11]; quinine which has antipyretics and antimalarial properties [12]; and reserpine which can be used to treat high blood pressure. Alkaloids are regarded as reserve materials for protein synthesis, as protective substances discouraging animal or insect attacks, and as plant stimulants or regulators or simply as detoxification products. Alkaloids currently in clinical use include the analgesics morphine and codeine, the anticancer agent vinblastine, the gout suppressant colchicine, the muscle relaxant tubocurarine, the antiarrhythmic ajmalicine, the antibiotic sanguinarine, and the sedative scopolamine.

In vitro studies have shown that natural phenols have antimicrobial [13], antiviral [14], anti-inflammatory [15], and vasodilatory actions [16]. It protects the plant against adverse factors

which threaten its survival in an unfavorable environment, such as drought, physical damage or infections. Resistance of plants to UV radiations is due to the phenolic compounds especially the phenylpropanoids present in them [17]. Phenolic compounds act as antioxidants protecting cells from oxidative stress scavenging of free radicals by hydrogen atom donation. The action of phenolic as neuroprotective [18], fungicidal [19], bactericidal [20] compounds and their anti-atherosclerosis [21] effects, and anticancer [22] activity is well documented.

Terpenoids are commercially important fragrance and flavoring agents [23]. Prenol and α-bisabolol are used in fragrance due to fruity odor and sweet floral aroma, respectively. Mono and sesqui terpenes are basis of natural perfumes and also of spices and flavorings in the food industry. The roles of terpenoids as pharmaceutical agents with activities such as antibacterial and antineoplastic are still under investigation. There are examples of diterpenes that exhibited *in vitro* cytotoxic, antitumor, and antimicrobial activities. Terpenes are vital for life in most organisms exerting metabolic control and mediating inter and intra species interactions, for example, manufacture compounds in response to herbivory or stress factors, and it has also been shown that flowers can emit terpenoids to attract pollinating insects and even attract beneficial mites, which feed on herbivorous insects. Cheng et al. [24] have reported that terpenes may act as chemical messengers influencing the expression of genes involved in plant defensive functions or influence gene expression of neighboring plants. Other secondary metabolite of plant origin and their functions is given in **Table 2** [25].

4.2. Production of secondary metabolites from plants

4.2.1. Conventional

The conventional method of secondary metabolite production relies on extraction of metabolite, not production, from the tissues of plant by different phytochemical procedures like solvent, steam, and supercritical extraction. The recent developments in biotechnological methods like plant tissue culture, enzyme and fermentation technology have facilitated *in vitro* synthesis and production of plant secondary metabolites. The major processes include:

4.2.2. Immobilization

Cell or biocatalysts are confined within a matrix by entrapment, adsorption or covalent linkage. On addition of suitable substrate and provision on optimum physico chemical parameters, the desired secondary metabolites are synthesized. Immobilization with suitable bioreactor system provides several advantages, such as continuous process operation, but for the development of an immobilized plant cell culture process, natural or artificially induced secretion of the accumulated product into the surrounding medium is necessary.

4.2.3. In vitro tissue, organ, and cell culture

Plant cell and tissue cultures can be established routinely under sterile conditions from explants, such as plant leaves, stems, roots, meristems, etc., both for multiplication and extraction of secondary metabolites. Shoot, root, callus, cell suspension, and hairy root culture are used to synthesize metabolite of interest. Metabolites which are localized in multiple tissues

S. No.	Secondary metabolites	Biological activity
1.	Pyrethrins	Insecticidal
2.	Nicotine	Insecticidal
3.	Rotenoids	Insecticidal
4.	Azadirachtin	Insecticidal
5.	Phytoecdysones	Insecticidal
6.	Baccharine	Antineoplastic
7.	Bruceantine	Antineoplastic
8.	Gsaline	Antineoplastic
9.	3-Doxycolchicine	Antineoplastic
10.	Ellipticine	Antineoplastic
11.	9-methoxyellipticine	Antineoplastic
12.	Fagaronive	Antineoplastic
13.	Tlarringtovinl	Antineoplastic
14.	Jandicine N-oxide	Antineoplastic
15.	Maytansive	Antineoplastic
16.	Podophyllotoxin	Antineoplastic
17.	Taxol	Antineoplastic
18.	Thalicarpine	Antineoplastic
19.	Tripdiolide	Antineoplastic
20.	Vinblastin	Antineoplastic
21.	Quinine	Antimalarial
22.	Digoxin	Cardiac tonic
23.	Diosgunin	Antifertility
24.	Morphine	Analgesic
25.	Thebaine	Source of codeine
26.	Suolpolanine	Antihypertension
27.	Alropine	Muscle relaxant
28.	Codeine	Analgesic
29.	Shikonin	Dye, pharmaceutical
30.	Anthroquinones	Dye, laxative
31.	Rosamarinic acid	Spice, antioxidant, perfume
32.	Jasmini	Sweetner
33.	Stevioside	Saffron
34.	Croun	Chili

S. No.	Secondary metabolites	Biological activity
35.	Capsacin	Vanilla
36.	Vanillin	Rubber
37.	Gutla percha	Essential oils
38.	Terpendids	Spasmolytic
39.	Papaverive	Hypertensive
40.	Ajmalicive	Stimulant
41.	Caffeine	Antispasmadic
42.	Birberine	NA

NA – Not Assessed.
Source: Ramawat and Merillon [25].

Table 2. Biological activities of some secondary metabolites of plants.

can be synthesized through unorganized callus or suspension cultures. But when the metabolite of interest is restricted to specialized part or glands in host plant, differentiated microplant or organ culture is the method of choice. Saponins from ginseng are produced in its roots, and hence *in vitro* root culture is preferred for saponin synthesis. Similarly, antidepressant hypericin and hyperforin are localized in foliar glands of *Hypericum perforatum*, which have not been synthesized from undifferentiated cells [26].

The quantum of secondary metabolite production in cell cultures can be enhanced by treating plant cells with biotic and/or abiotic elicitors. Methyl jasmonate, fungal carbohydrates, and yeast extract are the commonly used elicitors. Methyl jasmonate is an established and effective elicitor used in the production of taxol from *Taxus chinensis* [27] and ginsenoside from *Panax ginseng* [28–32]. The most recently evolved and designed metabolic engineering can be employed to improve the productivity.

The production of metabolites through hairy root system based on inoculation with *Agrobacterium rhizogenes* has garnered much attention of late. The quality and quantity of secondary metabolite by hairy root systems is same or even better than the synthesis by intact host plant root [33]. In addition, stable genetic make up, instant growth in plant tissue culture media san phytohormones provides additional scope for biochemical studies. Root tips infected with *A. rhizogenes* are grown on tissue culture media [Murashige and Skoog's (MS) Gamborg's B5 or SH media] lacking phytohormones. Srivastava and Srivastava [34] have recently summarized the attempts to adapt bioreactor design to hairy root cultures; stirred tank, airlift, bubble columns, connective flow, turbine blade, rotating drum, as well as different gas phase reactors have all been used successfully. Genetic manipulation in hairy root culture for secondary metabolite production is being tried out. The established roots are screened for higher growth and production of metabolites. Transgenic hairy roots generated though *Agrobacterium rhizogenes* have not only paved way for plantlet generation but also for synthesis of desired product through transgenic hairy root cultures.

4.3. Secondary metabolites of microorganisms

Microbial secondary metabolites are low molecular mass products with unusual structures. The structurally diverse metabolites show a variety of biological activities like antimicrobial agents, inhibitors of enzymes and antitumors, immune-suppressives and antiparasitic agents [7], plant growth stimulators, herbicides, insecticides, antihelmintics, etc. They are produced during the late growth phase of the microorganisms. The secondary metabolite production is controlled by special regulatory mechanisms in microorganisms, as their production is generally repressed in logarithmic phase and depressed in stationary growth phases. The microbial secondary metabolites have distinctive molecular skeleton which is not found in the chemical libraries and about 40% of the microbial metabolites cannot be chemically synthesized [35].

4.3.1. Features of microbial secondary metabolites

- The principle and process of natural fermentation product synthesis can be successfully scaled up and employed to maximize its application in the field of medicine, agriculture, food, and environment.
- The metabolite can serve as a starting material for deriving a product of interest, extended further through chemical or biological transformation.
- New analog or templates in which secondary metabolite serve as lead compounds will lead discovery and design of new drugs.

4.4. Applications of microbial secondary metabolites

4.4.1. Antibiotics

The discovery of penicillin initiated the researchers for the exploitation of microorganisms for secondary metabolite production, which revolutionized the field of microbiology [5]. With the advent of new screening and isolation techniques, a variety of β-lactam-containing molecules [36] and other types of antibiotics have been identified. About 6000 antibiotics have been described, 4000 from actinobacteria (**Table 3**). In the prokaryotic group, unicellular bacteria *Bacillus* (**Table 3**) and *Pseudomonas* (**Table 3**) species are the most recurrent antibiotic producers. Likewise in eukaryotes, fungi are dominant antibiotic producers next to plants (**Table 3**). In the recent years, myxobacteria and cyanobacteria species have joined these distinguished organisms as productive species.

The pharmaceutical product, especially anti-infective derivatives comprise 62% antibacterials, 13% sera, immunoglobulins, and vaccines, 12% anti-HIV antivirals, 7% antifungals, and 6% nonHIV antivirals. There are over 160 antibiotics. *Streptomyces hygroscopicus* with over 200 antibiotics, *Streptomyces griseus* with 40 antibiotics, and *Bacillus subtilis* with over 60 compounds are the major contributors to the antibiotic market [7].

4.4.2. Antitumor agents

Natural product and its derivatives account for more than 60% of anticancer formulations. Actinobacteria derived antineoplastic molecules currently in use are actinomycin D,

Name of secondary metabolites	Source of secondary metabolites	Biological activities	References
Secondary metabolites of Actinobacteria			
Resistomycin	*S. corchorusii*	HIV-1 protease inhibitor	Shiono et al. [39]
Himalomycins A and B	*Streptomyces* sp. B6921	Antimicrobial	Maskey et al. [40]
Bonactin	*Streptomyces* sp. BD21–2	Antibacterial	Schumacher et al. [41]
Trioxacarcins	*S. ochraceus* and *S. bottropensis*	Antitumor and antimalarial	Maskey et al. [42]
Chinikomycins A and B	*Streptomyces* sp.	Antitumor and antiviral	Li et al. [43]
Daryamides	*Streptomyces* sp. CNQ-085	Cytotoxic polyketides	Asolkar et al. [44]
Resistoflavine	*S. chibaensis*	Antibacterial	Gorajana et al. [45]
Chalcomycin A and terpenes	*Streptomyces* sp. M491	Antibacterial	Wu et al. [46]
Napyradiomycin (C-16 stereoisomers)	*S. antimycoticus*	Antibacterial	Motohashi et al. [47]
Oxohexaene and Cephalaxine	*Streptomyces* sp. RM17; *Streptomyces* sp. RM42	Antibacterial	Remya and Vijayakumar [48]
Citreamicin θ A, Citreamicin θ B, and Citreaglycon A	*S. caelestis*	Antibacterial	Liu et al. [49]
Spiramycin	*Streptomyces* sp. RMS6	Antibacterial	Vijayakumar and Malathi [50]
N-isopentyltridecanamide	*Streptomyces labedae* ECR 77	Antibacterial	Thirumurugan et al. [51]
Staurosporine	*Streptomyces champavatii* KV2	Antimicrobial	Cholarajan and Vijayakumar [52]
Secondary metabolites of *Bacillus* spp.			
Coagulin	*B. coagulans*	Bactericidal, Bacteriolytic	Le Marrec et al. [53]
Bacthurucin f4	*B. thuringenesis* sp.	Fungicidal sub sp., *kurstaki* BUPM4	Kamoun et al. [54]
Cerein	*B. cereus*	Bactericidal, bacteriolytic	Bizani et al. [55]
Megacin	*B. megaterium*	,	Lisboa et al. [56]
Thuricin S	*B. thuringenesis*	,	Chehimi et al. [57]
Thuricin CD 19	*B. thuringenesis DPC6431*	,	Rea et al. [58]
	B. anthracis		
Halobacillin 5b	*B. licheniformis*	Hemolytic, cytotoxic	Kalinovskaya et al. [59]
Bacillomycin	*B. amyloliquefacins* FZB42,	Antifungal hemolytic	Ramarathnam et al. [60]
	B. subtilis		
Bacilysocin	*B. subtilis*	Fungicidal, antibacterial	Tamehiro et al. [61]
Bacilysin 1	*B. subtilis* 168, *B. pumilus*	Antifungal, antibacterial	Steinborn et al. [62]
	B. amyloliquefaciens GSB272		

Name of secondary metabolites	Source of secondary metabolites	Biological activities	References
Secondary metabolites of *Pseudomonas* **spp.**			
Pseudomonine	*P. stutzeri* KC	Competitive inhibition of phytopathogens	Lewis et al. [63]
Hydrogen cyanide	*P. pseudoalcaligenes* P4	Antifungal	Ayyadurai et al. [64]
Secondary metabolites of Fungi			
Lovastatin	*Monascus ruber; Aspergillus terreus*	Enzyme inhibitor	Dewick [65]
Limonene and guaiol	*Trichoderma viride*	Antimicrobial	Awad et al. [66]
Tuberculariols	*Tubercularia* sp. TF5	Anticancer	Xu et al. [67]
Oxaline	*Penicillium raistricki*	Anti-cell proliferation	Sumarah et al. [68]
Benzomalvin C	*Penicillium raistrickii, Penicillium* sp. SC67	Antimalarial	Stierle et al. [69]
Roquefortine C	*P. roqueforti; P. crustosum*	Neurotoxin	Kim et al. [70]; Xu et al. [67]
Pravastatin	*Penicillium citrinum*	Anticholesterolemics	Gonzalez et al. [71]

Table 3. Secondary metabolites produced by microorganisms.

anthracyclines (daunorubicin, doxorubicin, epirubicin, pirarubicin, and valrubicin), bleomycin, mitosanes (mitomycin C), anthracenones (mithramycin, streptozotocin, and pentostatin), enediynes (calicheamicin), taxol, and epothilones [37].

Taxol is the nonactinobacterial molecule derived from plant *Taxus brevifolia* and endophytic fungi *Taxomyces andreanae* and *Nodulisporium sylviforme.* It interferes with microtubule breakdown, an essential event leading to cell division, thereby inhibiting rapidly dividing cancer cells. It is effective against breast and advanced form Kaposi's sarcoma. It is also found to exhibit antifungal activity against *Pythium*, *Phytophthora,* and *Aphanomyces*.

4.4.3. Pharmacological and nutraceutical agents

One huge success was the discovery of the fungal statins, including compactin, lovastatin, pravastatin, and others which act as cholesterol-lowering agents. Lovastatin is produced by *A. terreus.* Of great importance in human medicine are the immunosuppressants such as cyclosporin A, sirolimus (rapamycin), tacrolimus, and mycophenolate mofetil. They are used for heart, liver, and kidney transplants and were responsible for the establishment of the organ transplant field. Cyclosporin A is made by the fungus *Tolypocladium niveum*. Mycophenolate mofetil is a semisynthetic product of the oldest known antibiotic, mycophenolic acid, and is also made by a fungus. Sirolimus and tacrolimus are products of streptomycetes [7]. Metabolites of probiotic bacteria are considered as a remedy for controlling weight gain, preventing obesity, increasing satiety, prolonging satiation, reducing food intake, reducing fat deposition, improving energy metabolism, treating and enhancing insulin sensitivity, and

treating obesity. *Firmicutes* and *Bacteroidetes* are the dominant beneficial bacteria present in the normal human gastrointestinal tract, and the latter was reported in lower numbers in constipation-predominant irritable bowel syndrome patients [38]. Carotenoids of microbial origin are used as food colorant, fish feeds, nutraceuticals, cosmetics, and antioxidants. Food colorant widely used is carotene derived from *Blakeslea trispora, Dunaliella salina* and lycopene from *B. trispora* and *Streptomyces chrestomyceticus, subsp. rubescens.* Astaxanthin produced from *Xanthophyllomyces dendrorhous* is an approved fish feed. Astaxanthin, lutein, β-carotene, zeaxanthin, and canthaxanthin are used as nutraceuticals due to their excellent antioxidant property. Docosahexaenoic acid (DHA) used in infant formula as nutritional supplements is derived from microalgae *Schizochytrium* spp. [7].

4.4.4. Enzymes and enzyme inhibitors

Enzymes produced from microorganism have annual sales of US $ 2.3 billion enzymes that find application in detergents (34%), foods (27%), agriculture and feeds (16%), textiles (10%), and leather, chemicals, and pulp and paper (10%). The protease subtilisin used in detergents has an annual sale of $ 200 million. The other major enzymes include glucose isomerase (100,000 tons) and penicillin amidase (60,000 tons). Nitrilase (30,000 tons) and phytase are amounting for $135 million worth of production. *Streptomyces* glucose isomerase is used to isomerize D-glucose to D-fructose, to make 15 million tons per year of high fructose corn syrup, valued at $1 billion [7].

The most important enzyme inhibitors are clavulanic acid, synthesized by *Streptomyces clavuligerus*, the inhibitor of β-lactamases. Some of the common targets for other inhibitors are glucosidases, amylases, lipases, proteases, and xanthine oxidase. Amylase inhibitors prevent absorption of dietary starches into the body, and hence can be used for weight loss [38].

4.4.5. Agricultural and animal health products

Secondary metabolites find wide applications in the field of agriculture and animal health: kasugamycin and polyoxins are used as biopesticides; *Bacillus thuringiensis* crystals, nikkomycin, and spinosyns are used as bioinsecticides; bioherbicides (bialaphos) find application as bioherbicides; ivermectin and doramectin as antihelmintics and endectocides against worms, lice, ticks, and mites; ruminant growth promoters in the form of coccidiostats; plant hormones like gibberellins as growth regulators are the most common application [7].

4.5. Production of secondary metabolites from microorganisms

Secondary metabolites branch out from the pathways of primary metabolism. Commercially, important secondary and primary metabolic pathways are given in **Table 4**.

4.5.1. Liquid fermentation

Batch or fed-batch culture in submerged fermentation is employed for production of secondary metabolites. Inoculum is developed after careful strain improvement of producing organism. Initially, shake flasks culture is employed, and the culture which are in active growth

S. No.	Intermediates from primary metabolic pathway	Secondary metabolites derived
1.	Shikimic acid	Ergot alkaloids, antibiotics: candicidin and chloramphenicol
2.	Amino acids	Antibiotics: penicillin, cephalosporins and cephamycins, and gramicidin, immunosuppressive cyclosporine
3.	Acetyl-CoA and other Kreb's cycle intermediates	Antibiotics: erythromycin, antiparasitic avermectin antitumor doxorubicin, taxol
4.	Sugars	Antibiotics: streptomycin and kanamycin.

Table 4. Intermediate from primary metabolism and their secondary metabolite derivatives.

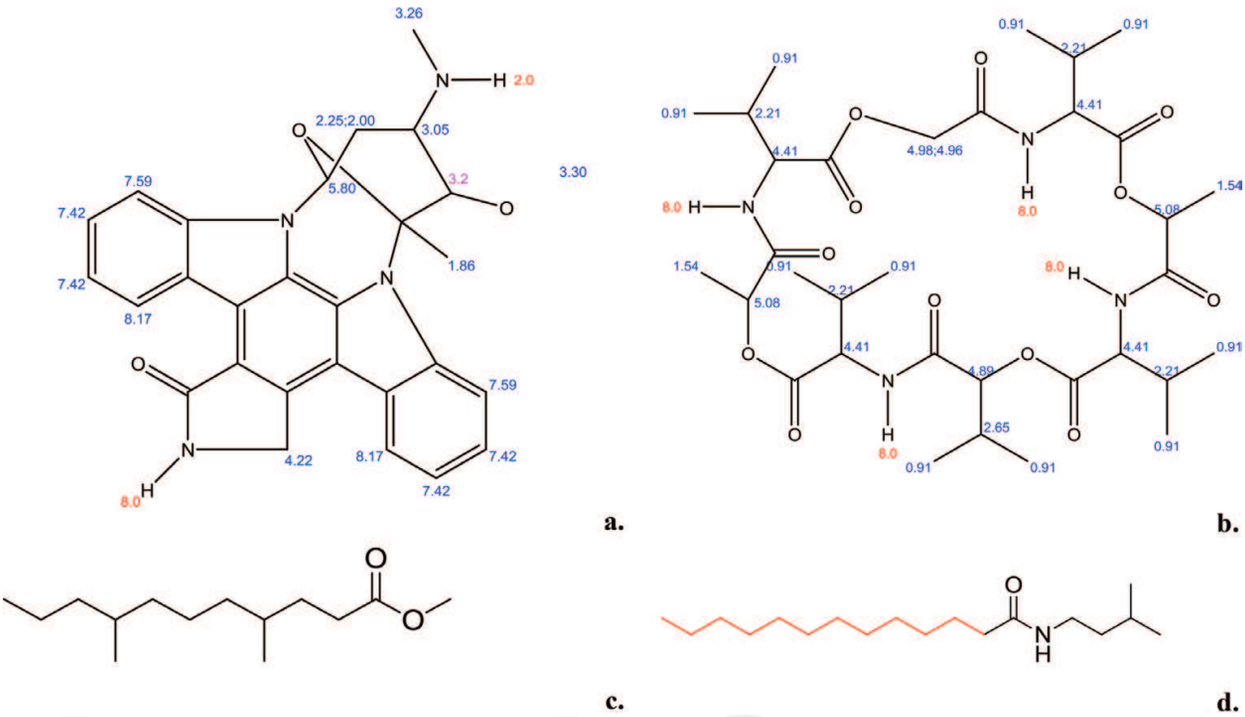


Figure 2. Chemical structures of actinobacterial secondary metabolites. (a) Staurosporine, (b) octa-valinomycin, (c) methyl-4,8-dimethylundecanate, and (d) N-isopentyltridecanamide from actinobacteria. Source: Cholarajan and Vijayakumar [52]; Cholarajan [72]; Thirumurugan et al. [73].

phase are transferred to a small fermenter and later into a larger fermenter with production medium. Several parameters, like medium composition, pH, temperature, and agitation and aeration rate, are controlled. An inducer such as methionine is added to cephalosporin fermentations, phosphate is restricted in chlortetracycline fermentation, and glucose is avoided in penicillin or erythromycin fermentation.

4.5.2. Solid-state fermentation

Solid-state fermentation, defined as a microbial culture that develops on the surface and at the interior of a solid matrix and in the absence of free water, holds an important potential for the production of secondary metabolites. Two types of SSF can be distinguished, depending on

the nature of solid phase used [7]: (a) solid culture of one support-substrate phase solid phase and (b) solid culture of two substrate-support phase solid phase. The advantages of solid-state fermentation in relation with submerged fermentation include: energy requirements of the process are relatively low, since oxygen is transferred directly to the microorganism. Secondary metabolites are often produced in much higher yields, often in shorter times, and often sterile conditions are not required [7].

It is important here to note our own experience of deriving actinobacterial secondary metabolite. Actinobacteria from terrestrial and marine habitats were screened for their antimicrobial activity. The bioactive metabolites were extracted and purified by thin layer and column chromatography, and the structure of the metabolite was elucidated by UV-spectrometry, FT-IR, mass spectrum analysis, and NMR. The derived metabolites staurosporine, octa-valinomycin, methyl-4,8-dimethylundecanate, and N-isopentyltridecanamide are known for their biological activity (**Figure 2**).

5. Conclusion

This review emphasizes the importance of secondary metabolites from various sources like plants, microorganisms including bacteria, actinobacteria, and fungi and its classification, production and applications in various fields. Since there is a constant and crucial requirement for new pharmaceutical agents to fight cancers, cardiac disorders, pests, cytotoxic, mosquitoes, infectious diseases, and autoimmune disorders of both animals and plants as climate changes provide conditions favorable to repeated outbreaks of these events. The battle against any disease is a vibrant symmetry between advances in chemotherapy and natural selection on infectious or invasive agents. If the scientific community is to put constant importance in this never ending effort, then new sources of bioactive secondary metabolites with novel activities must be found. Secondary metabolites are one of their essential means of growth and defense, and these metabolites are readily available for discovery. Secondary metabolites with noteworthy biological activity are considered as an alternative to most of the synthetic drugs and other commercially valuable compounds.

Author details

Durairaj Thirumurugan[1], Alagappan Cholarajan[2], Suresh S.S. Raja[3] and Ramasamy Vijayakumar[3]*

*Address all correspondence to: rvijayakumar1979@gmail.com

1 Department of Biotechnology, SRM Institute of Science and Technology, Tamilnadu, India

2 P.G. Department of Microbiology, Srinivasan College of Arts and Science, Perambalur, India

3 Research Department of Microbiology, Bharathidasan University Constituent College, Perambalur, India

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