

# Secondary Metabolites in Drug Development: Tracing Their Historical and Therapeutic Impact

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## Abstract

Secondary metabolites, also known as natural products, exhibit a level of structural and chemical diversity unmatched by synthetic small molecule libraries. These compounds, which have evolved to possess drug-like properties, continue to be a primary source for new medications and drug leads. Their discovery has significantly impacted advancements in chemistry, biology, and medicine, influencing drug development and therapeutic strategies throughout history. Derived from primary metabolic pathways such as photosynthesis, glycolysis, and the Krebs cycle, secondary metabolites are formed from the essential biosynthetic intermediates produced by these processes (Dewick, 2002). Plants and their extracts are composed of a diverse range of bioactive compounds or phytochemicals that vary in polarity. These phytochemicals form the basis for numerous pharmaceutical products. The specific components of a plant play a crucial role in identifying crude medicines, and they are typically associated with minimal adverse effects. Throughout history, humans have turned to nature, especially plants, in their search for new drugs. Consequently, many medicinal plants with therapeutic properties are now employed to treat various conditions. Historical records such as the Ebers Papyrus (circa 2900 B.C.) document approximately 700 plant-based remedies, such as gargles, pills, infusions, and ointments, which are listed in CITES Appendix II. Other ancient texts which provided extensive information on traditional medicinal plants, such as the Chinese Materia Medica with 52 formulas, the Shennong Herbal with 365 remedies, and the Tang Herbal with 850 drugs also detail the use of natural products. Given that only about 10% of global biodiversity has been explored for its potential biological activity, there remains a vast array of natural compounds yet to be discovered, highlighting the challenge of accessing this diverse chemical resource. Considering emerging diseases like cancers, AIDS, SARS, and bird flu, alongside growing environmental challenges, including biodiversity loss and land and water degradation, there is an urgent need to identify and isolate novel and beneficial molecules. These discoveries are crucial for addressing and mitigating various aspects of human health and environmental issues (Bacon and White, 2003).

**Keywords:** Natural product, secondary metabolites, photosynthesis, biodiversity, AIDS, medication, SARS, etc.

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## INTRODUCTION

Designed by nature for the welfare of other types of organisms, including humans, plants are the true wealth of the cosmos. Since the dawn of the human era, these plants have served as the basis for all of humanity's needs, including food, medicine, textiles, wood, oils, and resin [1]. Plants serve as a rich source of therapeutic compounds with minimal adverse effects [2]. Humans have sought novel drugs from nature, especially plants, since ancient times. Consequently, a wide array of medicinal plants with therapeutic properties is now utilized to address various health issues [3]. Today,

about 80% of the global population relies on traditional medicines, which frequently utilize plant extracts for their primary health care needs. Phytochemical compounds such as alkaloids, flavonoids, terpenes, and glycosides are fundamental to many pharmaceutical industries. These plant components play a crucial role in defining the identity of crude medicines [3]. Natural products, categorized as primary and secondary metabolites, are bioactive substances derived from plants, animals, and microorganisms [4].

According to Dewick (2002), primary metabolism is the creation and degradation of proteins, lipids, nucleic acids, and carbohydrates, which are necessary to all living organisms, with the molecules participating in the pathways referred to as “primary metabolites”. Also, Bernardini et al. [4] elaborated that plant natural products, also referred to as secondary metabolites, are byproducts of gene expression that are typically not essential for the plant’s reproduction, growth, or development. Instead, these compounds are produced as adaptations to environmental factors or as defensive mechanisms against predators, enhancing the plant’s survival [5]. Key intermediates such as acetyl coenzyme A (acetyl-CoA), shikimic acid, mevalonic acid, and 1-deoxysilulose-5-phosphate. It plays an important role in the formation of these secondary metabolites. These intermediates participate in various biosynthetic pathways involving multiple reactions such as alkylation, decarboxylation, aldol, Claisen, and Schiff base reactions (Dewick, 2002). The population are in large part dependent on forests for grazing, gasoline, fodder, timber, medicinal, and wild fit to be eaten plant life, making agricultural tools, and so on. Due to continuous use of economically crucial species, their populations are depleting unexpectedly, and habitat degradation has multiplied many folds. Besides these, medicinal plants are substantially used in the traditional structures of medicines [6].

## HISTORICAL BACKGROUND OF MEDICINAL PLANTS

Plants have been used medicinally since ancient times. The burial of a neanderthal man who was buried 60,000 years ago contained evidence of this early relationship. The several plants buried alongside the deceased were all identified by pollen analysis as having medical potential. The oldest known medical record is a 4000-year-old clay tablet from Sumerian culture that lists plant treatments for several diseases [7]. Information regarding the first therapeutic applications of plants can also be found in ancient China.

The legendary Chinese emperor Shen-Nung, who lived over 4500 years ago, was credited with creating numerous of herbal remedies. These remedies were later compiled in the *Pun-Tsao*, a pharmacopoeia published in 1600 [7] described that after the Columbus expedition many new world plants were exported to Europe. By the reign of King Henry VIII in England (1491–1547), a comprehensive system that blended plant use with astrology had emerged. Historically, herbal medicine has been a core part of western medical practice [7]. Hippocrates, regarded as the “Father of Medicine,” lived between 460 and 377 B.C. and incorporated various herbs into his treatments, emphasizing the natural causes of diseases [7]. In *De Materia Medica*, which included a description of more than 600 kinds of plants with therapeutic significance, along with explanations and drawings of the plants, it also provided instructions on how to prepare, utilize, and monitor the medications and their deleterious effects [7].

The Ebers Papyrus, which dates to about 1550 B.C. contains important information on over 700 plant medicines such as tablets, ointments, and infusions. Other important ancient texts include the *Chinese Materia Medica* (1100 B.C.), the *Shennong Herbal* (100 B.C.), and the *Tang Herbal* (659 A.D.), each listing numerous plant-based remedies [5] have all been thoroughly chronicled throughout thousands of years [8]. Ayurveda practices have been recorded since the first millennium BC [9–22]. Nature has been a source of medicinal compounds since ancient times and today there are a surprising number of medicines that are derived from natural sources based on their traditional medical use [9]. Theophrastus, a philosopher and natural scientist who lived around 300 B.C., discussed the therapeutic properties of plants in his book “History of Plants” and made note of how cultivation

could alter a plant's traits [9]. Galen (130–200 A.D.) is renowned for his intricate prescriptions and formulas used in compounding pharmaceuticals, often involving dozens of constituents (“galenicals”). Galen practiced and taught pharmacy and medicine in Rome and wrote more than 30 books on these subjects [9]. William Withering conducted one of the first systematic studies on folk medicine. His research on foxglove as a remedy for dropsy (congestive heart failure) between 1775 and 1785 established the benchmark for medicinal chemistry [7].

### PLANT DERIVED SECONDARY METABOLITES

There is a long history of traditional medicine helping people all around the world. In China and other places, indigenous medical systems heavily rely on medicinal plants [7, 8]. Highlighted that only about 10% of the world's biodiversity has been evaluated for biological activity, leaving many potential natural compounds yet to be discovered. One major challenge is gaining access to this chemical diversity. Oils extracted from plants like *Cupressus sempervirens* (Cypress) and *Commiphora* species (myrrh), used for treating colds and inflammation, have been mentioned on ancient Mesopotamian tablets from 2600 B.C. [8]. During the Middle Ages, monasteries in Europe preserved the knowledge of Greco-Roman medicinal practices, while Arab scholars introduced new herbs and methods to the west. They were also the first to establish independent pharmacies [8, 10]. Highlighted that only about 10% of the world's biodiversity has been evaluated for biological activity, leaving many potential natural compounds yet to be discovered. In hot weather, the plant *Alhagi maurorum* produces a sweet and sticky substance from its stems and leaves [11]. Known as “manna”, this substance mainly consists of melecitose, sucrose, and invert sugar. It has been used to treat many diseases such as anorexia, constipation, skin diseases, nosebleeds, fever, leprosy, and obesity [10]. In Israel, the roots were boiled to treat bloody diarrhea, while the Konkani people smoked the plant to ease asthma. Used by the Romans to treat nasal polyps native to northern Europe and eastern North America *Ligusticum scrotum* Linnaeus is thought to protect against everyday infections when consumed raw in the morning. Additionally, its root was used as a remedy for flatulence, an aphrodisiac, and a sedative in the Faeroe Islands [12].

Butler (2004) explained that many early medicines were rooted in traditional practices, which were subsequently refined through research in clinical, pharmacological, and chemical studies. For instance, acetylsalicylic acid (*aspirin*) was synthesized from salicin, a natural compound found in the bark of the *willow tree* (*Salix alba L.*) [13, 14]. The discovery of morphine was also facilitated by the extraction; the extraction of alkaloids from the opium poppy (*Papaver somniferum L.*) led to the discovery of morphine [10] a commercially valuable medication originally described in 1803. In the 1870s, crude morphine extracted from the *P. somniferum* herb was hydrolyzed with acetic anhydride to produce diacetylmorphine (heroin), which was soon converted to the painkiller codeine. Poppy extracts were used medicinally by the Sumerians and ancient Greeks in ancient times. Although addictive in Arabs due to its opium-like properties [15, 16]. *Digitalis purpurea L.*, also known as foxglove, was popular in Europe throughout the 10th century because of its main ingredient, digitoxin, a glycoside. It was not discovered until the late 19th century [17]. Long used to treat congestive cardiac failure, *digoxin* [10] and its counterparts; however, because to potential long-term adverse reactions, these medications are gradually being replaced with novel medications for “heart failure” [15].

Quinine is an antimalarial drug made from the bark of *Cinchona succirubra* Pav *ex Klotsch* along with FDA approval in 2004, has been used for thousands of years to treat carcinoma, constipation, a high temperature, the parasite malaria, and oral and vocal ailments, according to Butler (2004). When the British started growing the plant all over the world in the middle of the 1800s, this bark was originally utilized to cure malaria [15]. For more than a century, the *L-histidine*-derived alkaloid pilocarpine [10] found in *Pilocarpus jaborandi* (Rutaceae) has been used as a medicinal drug to treat acute angle-closure glaucoma as well as chronic open-angle glaucoma [18, 19]. Stated that the FDA permitted an oral version of *pilocarpine* in 1994 to alleviate mouth dryness (xerostomia), an adverse

consequence of radiation treatments for carcinomas of the head and neck, and to stimulate salivary glands to measure the levels of salt and chloride. Beginning with subsidiaries of a Malaysian gum tree, chemists found a chemical in 1991 that inhibits the virus responsible for AIDS to spreading in human cells [7]. Some of the antibiotics discovered during and after World War II are still in use. These were created based on the antibacterial properties of numerous naturally occurring substances that were identified from *Penicillium*, *Cephalosporium*, and *Streptomyces* species. Few novel medications came to light from higher plants in the years following World War II, with the significant exceptions being *vinblastine* via *Catharanthus roseus*, known to be effective in treating cancer, and reserpine obtained from *Rauwolfia* different species, which marked the dawn of tranquilizers [7]. A new paradigm in the development of drugs is the productive clinical agents that come from pharmaceuticals and synthesis cross-disciplinary studies. Examples of these agents include ACE-inhibitors and betablockers like *atenolol* and *captopril* for treating hypertension; adrenoceptor stimulants like *salbutamol* for asthma, and *benzodiazepines*, that is, hypnotics and anxiolytics for treating insomnia as well as anxiety attacks [7].

*Reserpine*, an antihypertensive substance derived from *Rauwolfia serpentina*, has been utilized in Ayurvedic medicine to treat snakebites and other conditions [20]. *Ephedrine*, initially discovered in 1887 from *Ephedra sinica* (Ma Huang), was utilized in traditional Chinese medicine and served as the starting material for the creation of *salbutamol* and *salmeterol*, two anti-asthma medications (beta agonists). Curare, an arrow poison employed by native communities in the Amazon, is made from the muscle relaxant tubocurarine, which was isolated from *Chondrodendron* and *Curarea* species [21]. It is clear how important traditional medicinal plants are and what potential new medication leads they represent. Over 200 corporations and academic institutions are reportedly screening plant and animal molecules for therapeutic qualities as of the mid-1990s. Research on medicinal plants has led to the development of a number of significant medications used in modern medicine, including *vinblastine*, *vincristine*, *topotecan*, *irinotecan*, *etoposide*, *teniposide*, and *taxol/paclitaxel* [7].

A possible antidiabetic drug has been isolated from a *Pseudomassaria* fungus species found in the Congo rainforest, according to a recent publication [10]. Approximately 62 percent of the 92 anticancer medications that were licenced globally between 1983 and 1994 and were commercially available in the United States before that time can be attributed to their natural origins [22]. Twelve orally active medicines that were approved by the FDA between 2014 and 2016 are shown in the Journal of Medicinal Chemistry. Based on molecular weights, six of these medications were used for the treatment of HCV, four were anticancer medicines, one was for chemotherapy nausea, and one was for cardiovascular treatment [14]. So, today's combining of traditional knowledge of medicinal plants with cutting-edge research initiatives offers a fresh perspective that significantly increases the rate of drug discovery compared to random collecting [7, 23].

## CONCLUSION

Research and development in natural drug discovery stand to gain significantly from ethnobotany and the study of common flora. Recently, there has been a renewed interest in applying traditional medicinal knowledge to plant research, reflecting a growing respect for indigenous and national rights over these resources. Despite increased scrutiny of western approaches to this data, both academic and industrial researchers now recognize the importance of these traditional insights. Medicinal plants globally have been subjected to pharmacological testing, highlighting their vital role in identifying new drug leads with substantial economic and medicinal value. The foundation of modern pharmaceuticals often involves the use of plants, plant extracts, and isolated compounds derived from natural sources. Consequently, the exploration of natural products has prompted a more systematic approach to discovering new bioactive substances from nature.

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