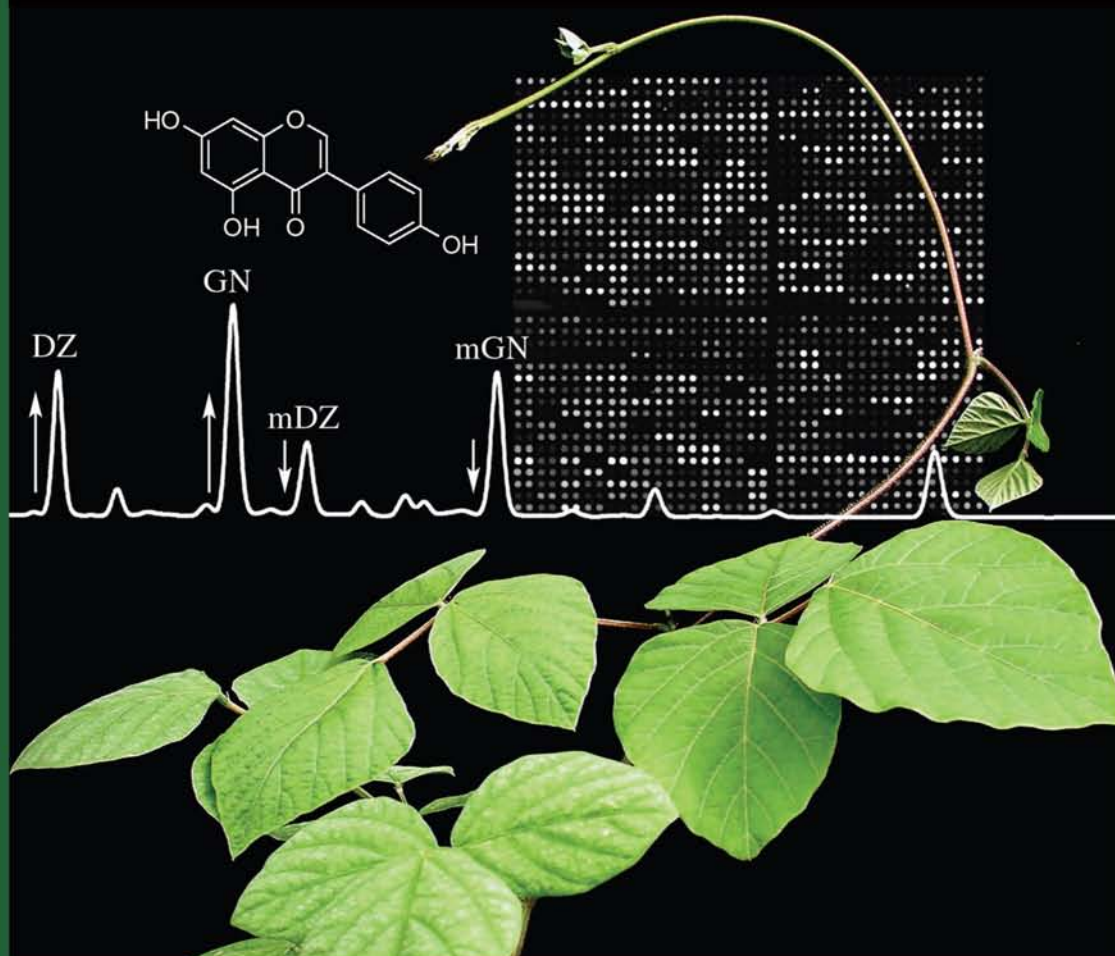


Natural Products from Plants

Second Edition



Leland J. Cseke, Ara Kirakosyan, Peter B. Kaufman
Sara L. Warber, James A. Duke, and Harry L. Brielmann

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Dedication

We dedicate this book to Steven F. Bolling, M.D., the first Gayle Halperin Kahn Professor of Integrative Medicine at the University of Michigan, as well as all the other pioneering individuals who have devoted their lives to the study, application, and conservation of plants.

Preface

As a result of teaching many undergraduate and graduate students about plant natural products in a wide range of plant biology courses, the need for a comprehensive yet thorough collection of information on what kinds of natural products plants produce, including why they produce them, became very apparent. Currently, such information is contained within thousands of somewhat disjointed reports about the helpful qualities and toxic effects of different plant species throughout the world. The aim of this second edition of the book is to help bring more unity and understanding to this complicated and often contradictory jumble of information. We updated and revised previously presented information and added more than 50% new topics that deal with plant natural product biochemistry, biotechnology, and molecular biology, as well as new separation techniques and bioassays.

This book is useful to many, including biochemists, natural product chemists, pharmacologists, pharmacists, and molecular biologists; research investigators in industry, federal labs, and universities; physicians, nurses, nurse practitioners, and practitioners of integrative medicine; premedical and medical students; ethnobotanists, ecologists, and conservationists; nutritionists; organic gardeners and farmers; those interested in herbs and herbal medicine; and even lawyers. With the growing interest in this field by professionals and the general public alike, it was important for us to produce a book that encompasses as much information as possible on the natural products produced by plants as well as their importance in today's world. We hope that this book helps to meet this need.

Some of the most compelling reasons for writing a book on natural products in plants include the following:

- While there has been a great deal of progress made in understanding plant natural products, a general lack of knowledge and much misinformation remain about natural products in plants and their uses by people.
- Many of the natural products in plants of medicinal value offer us new sources of drugs that have been used effectively for centuries in traditional medicine. Many compounds used in medicine today have original derivatives that were of plant origin.
- Plants are sources of poisons, addictive drugs, and hallucinogens. These have importance in human medicine and in human social action and behavior.
- Many people are interested in using natural products from plants for preventive medicine, but these people must be made aware of potential harmful effects of such compounds.
- Plants provide us with thousands of novel compounds that give us medicines, fragrances, flavorings, dyes, fibers, foods, beverages, building materials, heavy metal chelators important in bioremediation, biocides, and plant growth regulators.
- Knowledge about how and why plants produce such a vast array of metabolites gives us new insights into how plants use these compounds to deter predators and pathogens, attract and deter pollinators, prevent other plants from competing with themselves for the same resources, and defend themselves against environmental stress.

This book was organized to provide relevant and practical information on each of the above topics. It begins with a discussion of the various types of compounds found in plants (Chapter 1). We then discuss how and why these compounds are made by plants (Chapter 2). In Chapter 3, we consider how the synthesis of these compounds is regulated by environmental stresses, biotic factors, biochemical regulators, and gene expression to provide a better understanding of how these compounds benefit the plants themselves. Seven new chapters following Chapter 3 were added in this new edition of the book: Chapter 4 provides information about plant natural products in the rhizosphere (plant root–soil interface

regions). Chapter 5 covers examples of the molecular biology of natural products. In Chapter 6, we discuss natural product biosynthesis in the pregenomics and genomics eras. A new Chapter 7 deals with plant biotechnology for the production of natural products. Chapters 8, 9, and 10, respectively, guide the reader through analytical and preparative separations of natural products, how natural products are characterized, and bioassays for activity of natural products. In Chapter 11, we discuss the modes of action of natural products at target sites, using classic examples from medicine and cell biology. Chapter 12 includes information on the uses of plant natural products by humans and the risks associated with their use. The principle of synergy between separate kinds of compounds from a single plant source and from more than one plant source is discussed in Chapter 13. Chapter 14 takes a global view of various strategies that are used to conserve plants that produce natural products of value to humans. Finally, in a new Chapter 15, we address the relationship between people and plants.

The individual chapters of this book are organized according to the following format: chapter title, chapter outline, introduction to the chapter, chapter topics and text, conclusions (take-home lessons), and references cited for further reading. In addition, some of the chapters contain boxed essays written by experts in the field to bring diversity to the topics. We chose this format in order to aid the reader in comprehending the material and to stimulate one to probe the chapter topics further. The Appendix to this book (“Information Retrieval on Natural Products in Plants”) helps one to embark on the latter endeavor.

Regarding terminology pertaining to plant metabolites, we often encounter the terms “primary metabolite” and “secondary metabolite” in the literature. Traditionally, *primary metabolite* refers to nucleic acids, amino acids, proteins, lipids, carbohydrates, and various energetic compounds falling within the primary metabolic pathways of each cell. These compounds are essential for plant growth, development, reproduction, and survival. *Secondary metabolite* is a term that was originally coined to describe compounds that were not thought, at the time, to be essential to plant function. This old idea, however, cannot be defended on strictly chemical grounds, because, apparently, all natural products produced by plants have some survival value to the plant. Thus, the modern use of the term “secondary metabolite” typically refers to those compounds of low molecular weight that are often restricted to specific plant families and genera. These compounds may be important for pollination, attraction and deterrence of predators, or defense against pathogenic fungi and bacteria, or they may be essential for plant survival in stressful environments.

In this book, we attempt to avoid the terminology of “primary” and “secondary” by using simply “metabolite,” “product,” or “compound” wherever possible. However, because the traditional terms “primary metabolite” and “secondary metabolite” are still used widely in the literature as acceptable terminology, we continue to use them when we refer to “secondary metabolism” in the traditional sense (see Chapters 4, 6, and 7 for examples).

The Editors

Leland J. Cseke, Ph.D., earned a doctorate in plant cellular and molecular biology through the Department of Molecular, Cellular, and Developmental Biology at the University of Michigan, Ann Arbor. His dissertation research included the molecular biology, evolution, and biotechnological applications of terpenoid scent compound production in *Clarkia* and *Oenothera* species in the laboratory of Dr. Eran Pichersky. Currently, Dr. Cseke is a research assistant professor in the Department of Biological Sciences at the University of Alabama, Huntsville, where he works in conjunction with Dr. Gopi K. Podila in a large team effort to determine the molecular mechanisms of keystone species in forest ecosystem responses to environmental perturbations. The DOE-funded project represents an “Integrated Functional Genomics Consortium to Increase Carbon Sequestration in Poplar Trees” through the study of aspen Free-Air Carbon dioxide Enrichment (aspen FACE research). In addition, Dr. Cseke investigates the activity of aspen (*Populus tremuloides*) MADS-box genes in wood development. Similarly, Dr. Cseke spent several years as a research assistant professor at Michigan Technological University working to discover the functionality of floral-specific MADS-box genes in aspen flower development. Dr. Cseke was also a postdoctoral fellow in the Department of Plant Sciences at the University of Arizona in the laboratory of Dr. Rich Jorgensen. There, he worked to elucidate the factors involved in functional sense and antisense suppression of genes involved in anthocyanin biosynthesis. Dr. Cseke’s interests include the biosynthesis of plant chemical products, their uses by humans, and the study of the global effects of transgenes on plant metabolism. This led to his coauthoring the first edition of *Natural Products from Plants* (CRC Press, 1999). In addition, Dr. Cseke has done some work in the study of possible methods for improving separation and enhancing the biosynthesis of the cancer-fighting diterpene, taxol, in *Taxus* species in the laboratory of Dr. Peter Kaufman, and his knowledge of such subjects has been directed toward the teaching of classes emphasizing biotechnology and the chemical principles of biology.

Ara Kirakosyan, Ph.D., is associate professor of biology at Yerevan State University, Armenia, and is currently research investigator at the University of Michigan Integrative Medicine program (UMIM). He received a Ph.D. in molecular biology from Yerevan State University, Armenia in 1993. His research fields focus on the phytochemistry and molecular biology of medicinal plants. His research interests include plant cell biotechnology to produce enhanced levels of medicinally important secondary metabolites, and metabolic engineering based on the integration of functional genomics, metabolomics, transcriptomics, and large-scale biochemistry. He carried out postdoctoral research in the Department of Pharmacognosy at Gifu Pharmaceutical University, Gifu, Japan, under the supervision of Prof. Kenichiro Inoue. The primary research topic was molecular biology of glycyrrhizin and a sweet triterpene and unraveling an oxidosqualene synthase gene encoding β -amyirin synthase in cell cultures of *Glycyrrhiza glabra*. In addition, he held several research investigator positions in Germany. The first was under collaborative grant project DLR, at Heinrich-Heine-University, Düsseldorf. The research concerned a lignan anticancer project (the production of cytotoxic lignans from *Linum* [flax]) under the supervision of Prof. Dr. W.A. Alfermann. The second involved a carbohydrate-engineering project, as he was a DAAD Fellow in the Institute of Plant Genetics and Crop Plant Research (IPK) Gatersleben, under the supervision of Prof. Dr. Uwe Sonnewald. Another collaborative grant project on plant cell biotechnology involved the production of dianthrone in cell/shoot cultures of *Hypericum perforatum* (St. John’s wort); this project was carried out with Dr. Donna Gibson at the U.S. Department of Agriculture (USDA), Agricultural Research Service, Plant Protection Research Unit, U.S. Plant, Soil, and Nutrition Laboratory, Ithaca, NY. In 2002, he was a Fulbright Visiting Research Fellow at the University of Michigan, Department of Molecular, Cellular, and Developmental Biology in the Laboratory of Prof. Peter Kaufman. Dr. Kirakosyan is author of several chapters in five books and principal author of more than 50 peer-reviewed research publications. Dr. Kirakosyan is a full member of the Phytochemical Society of

Europe and the European Federation of Biotechnology. He received several awards, fellowships, and research grants from the United States, Japan, and the European Union.

Peter B. Kaufman, Ph.D., is a professor of biology emeritus in the Department of Molecular, Cellular, and Developmental Biology (MCDB) at the University of Michigan and is currently senior scientist, University of Michigan Integrative Medicine program (UMIM). He received his B.Sc. in plant science from Cornell University in Ithaca, New York, in 1949 and his Ph.D. in plant biology from the University of California, Davis, in 1954 under the direction of Professor Katherine Esau. He did postdoctoral research as a Muellhaupt Fellow at Ohio State University, Columbus. He has been a visiting research scholar at the University of Calgary, Alberta, Canada; University of Saskatoon, Saskatoon, Canada; University of Colorado, Boulder; Purdue University, West Lafayette, Indiana; USDA Plant Hormone Laboratory, BARC-West, Beltsville, Maryland; Nagoya University, Nagoya, Japan; Lund University, Lund, Sweden; International Rice Research Institute (IRRI) at Los Baños, Philippines; and Hawaiian Sugar Cane Planters' Association, Aiea Heights. Dr. Kaufman is a fellow of the American Association for the Advancement of Science and received the Distinguished Service Award from the American Society for Gravitational and Space Biology (ASGSB) in 1995. He served on the editorial board of *Plant Physiology* for 10 years and is the author of more than 220 research papers. He has published eight professional books to date and taught popular courses on Plants, People, and the Environment, Plant Biotechnology, and Practical Botany at the University of Michigan. He received research grants from the National Science Foundation (NSF), the National Aeronautics and Space Administration (NASA), the U.S. Department of Agriculture (USDA) BARD Program with Israel, National Institutes of Health (NIH), Xylomed Research, Inc., and Pfizer Pharmaceutical Research. He produced, with the help of Alfred Slote and Marcia Jablonski, a 20-part TV series entitled, "House Botanist." He was past chairman of the Michigan Natural Areas Council (MNAC), past president of the Michigan Botanical Club (MBC), and former Secretary-Treasurer of the American Society for Gravitational and Space Biology (ASGSB). He is currently doing research on natural products of medicinal value in plants at the University of Michigan Medical School in the laboratory of Stephen F. Bolling, M.D., and serves on the research staff of UMIM.

Sara Warber, M.D., is a family physician with a long-standing interest in botanical medicine that predates her entrance into medical school. She completed a combined residency and fellowship in family medicine at the University of Michigan. She was a Robert Wood Johnson Clinical Scholars Program Fellow at the university. She is currently co-director of UMIM (University of Michigan Integrative Medicine program) and assistant professor in the Department of Family Practice Medicine at the University of Michigan. Her interests include research into the safe and efficacious use of herbal medicines. She is collaborating on research and education related to the use of other complementary and alternative modalities in the optimization of health. In addition, Dr. Warber is designing community-oriented research to facilitate improved health through better understanding of cultural dimensions and traditional ways of healing. She lives with her husband and two sons in the Ann Arbor, Michigan area and enjoys spending time in the many remaining wild habitats surrounding the Great Lakes.

James A. Duke, Ph.D., retired from the USDA where he served as an economic botanist for 30 years. In retirement, he served five years with Nature's Herbs and two years with Allherb.com. He is an adviser to or trustee for the Amazon Center for Environmental Education and Research (ACEER), American Botanical Council (ABC), and conducts ecotours in Maine and Peru. He is the author of more than 25 books, the best seller, *The Green Pharmacy* (now in six languages); his most recent, the *CRC Handbook of Medicinal Plants* (second edition); and the *CRC Handbook of Medicinal Spices*. Dr. Duke graduated Phi Beta Kappa from the University of North Carolina at Chapel Hill in 1961 and was awarded a distinguished alumnus award in 2002. Before joining the USDA, he spent several years in Central and South America studying neotropical ethnobotany and living with various ethnic groups while closely observing their deep dependence on forest products. He is very interested in natural foods and nutritional approaches to preventive medicine and spent 2 years advising the Designer Food Program at the National Institutes of Health (NIH) and 5 years with the National Cancer Institute's (NCI) cancer screening

program. He is a popular lecturer on the subjects of ethnobotany, herbs, medicinal plants, and new crops and their ecology, and has taped dozens of TV and radio shows. Dr. Duke is now an emeritus adjunct professor in herbal medicine at the Tai Sophia Institute, which frequently holds classes in his Green Pharmacy Garden, Fulton, Maryland, where he grows more than 300 medicinal plants. The USDA maintains his very useful phytochemical and ethnobotanical databases online (www.ars-grin.gov/duke/).

Harry Briemann, Ph.D., received his Ph.D. in synthetic organic chemistry from Wesleyan University, Middletown, Connecticut, in 1994. He spent the following year investigating marine natural products as a postdoctoral fellow for Professor Paul Scheuer. His next postdoctoral position was in the area of organometallic chemistry for Professor John Montgomery at Wayne State University, Detroit. Dr. Briemann then spent 7 years (1998 to 2005) as a medicinal chemist at Neurogen Corporation in Branford, Connecticut. Dr. Briemann currently teaches chemistry at Glastonbury High School in Glastonbury, Connecticut.

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1

Phytochemicals: The Chemical Components of Plants

Harry L. Brielmann, William N. Setzer, Peter B. Kaufman, Ara Kirakosyan,
and Leland J. Cseke

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1.1 Introduction

Phytochemicals, as the word implies, are the individual chemicals from which plants are made. In this chapter, we will look at these materials, specifically, the organic components of higher plants. Numerous journals, individual books, and encyclopedic series of books have been written on this subject. The goal here is to review this area in a concise format that is easily understandable. The reader not familiar with chemistry may be somewhat intimidated by the material presented here. However, we believe that understanding the chemical composition of plants is a prerequisite to understanding many of the remaining topics of this book. This is especially true for material covered in Chapters 2 and 3. For those interested in reviewing a specific area in greater detail, the references section includes numerous citations for each organic group covered.

During the course of this survey, several themes will be emphasized. These include (1) the rich diversity of chemical structures known to be synthesized by plants through an amazingly diverse network of metabolic pathways (see Figure 2.1 in Chapter 2); (2) basic differences in the chemical properties of the compounds; (3) adaptive functions of these compounds for plants; (4) uses of the compounds by humans (see essays below); and (5) examples of typical plants (listed by common name and scientific binomial name) that contain the respective types of compounds. Often, these will be derived from common plants with which most of us are familiar. Some marine algal plants are also included, because they contain many truly unique bioactive molecules.

The general categories of plant natural products are organized very broadly in terms of increasing **oxidation state**. This begins with the lipids, including the simple and functionalized hydrocarbons, as well as the terpenes, which are treated separately. Following this are the unsaturated natural products, including the polyacetylene and aromatic compounds. We then cross over into the realm of the primarily hydrophilic molecules, including the sugars, and continue with those that can form salts, including the alkaloids, the amino acids, and the nucleosides. Overall, this scheme provides a simple organizational pattern for discussing the phytochemicals. It is consistent with the way that chemists often categorize organic chemicals in general and is roughly equivalent to a **normal-phase chromatographic analysis** of a given plant species. Like any organizational scheme for this subject, be it taxonomic, phylogenetic, or biochemical, it should only serve as a rough guide.

Essay on Phytochemicals of Medicinal Value in Plants

In common usage today, many phytochemicals are associated with health benefits. They have a long history, which continues today, as medicines (Rouhi, 2003b). Many, though not all, of these materials are classified as **secondary metabolites**. This terminology suggests, often incorrectly, that they are not essential for the normal growth, development, or reproduction of the plant. Numerous journals, individual books (Robinson, 1991; Bruneton, 1999; Duke, 1992), dictionaries (Buckingham, 2005), and databases (Duke, 2005) were dedicated to plant natural products. Journals in natural products chemistry recognized by the **American Society of Pharmacognosy** include *Chemistry of Natural Compounds* (Russian), *Economic Botany*, *Fitoterapia*, *Journal of Antibiotics*, *Journal of Asian Natural Products Research*, *Journal of Essential Oil Research*, *Journal of Ethnopharmacology*, *Journal of Natural Products*, *Journal of Natural Remedies*, *Natural Products Letters*, *Natural Products Reports*, *Natural Toxins*, *Nigerian Journal of Natural Products and Medicines*, *Pharmaceutical Biology* (note name change from *International Journal of Pharmacognosy*), *Phytochemical Analysis*, *Phytochemistry*, *Phytochemistry Reviews*, *Phytomedicine*, *Phytotherapy*

Research, Planta Medica, Toxicon, and Zeitschrift für Naturforschung. Professional societies dedicated to research on phytochemistry include the American Society of Pharmacognosy (www.phcog.org), the Phytochemical Society of Europe (www.dmu.ac.uk/ln/pse/psetoday.htm), AFERP (Association Francaise pour l'Enseignement et al Recherche en Pharmacognosie; www.aferp.univ-rennes1.fr/aferpnouveau/index.htm), the Phytochemical Society of North America (www.ucalgary.ca/~dabird/psna), and the Society of Medicinal Plant Research (www.ga-online.org), among others.

Essay on Natural Products and Commercial Medicines (Rouhi, 2003a)

Natural products have, until recently, been the primary source of commercial medicines and drug leads. A recent survey revealed that 61% of the 877 drugs introduced worldwide can be traced to or were inspired by natural products. However, beginning in the 1990s, natural product drug discovery was virtually eliminated in most big pharmaceutical companies. This was primarily due to the promise of the then-emerging field of combinatorial chemistry (Cseke et al., 2004), whereby huge libraries of man-made small molecules could be rapidly synthesized and evaluated as drug candidates.

Thus far, this approach has led to lukewarm results at best. From 1981 to 2002, no combinatorial compounds became approved drugs, although several are currently in late-stage clinical trials. At the same time, the number of new drugs entering the market has dropped by half, a figure of which the large pharmaceutical corporations are painfully aware. The haystack is larger, but the needle within it is more elusive. This has led only recently to a newfound respect for the privileged structures inherent within natural products (DeSimone et al., 2004).

Of the roughly 350,000 species of plants believed to exist, one-third of those have yet to be discovered. Of the quarter million that have been reported, only a fraction of them have been chemically investigated. Many countries have become aware of the value of the biodiversity within their borders and have developed systems for exploration as well as preservation. At the same time, habitat loss is the greatest immediate threat to biodiversity (Frankel et al., 1995; see also Chapter 14).

1.2 Lipids and Derivatives

Lipids are often defined as water-insoluble biomolecules that are soluble in nonpolar solvents (Bruice, 2004). This is a convenient definition because it encompasses a large area of chemical space, including many types of compounds that are otherwise hard to classify. There are two problems with this definition. First, given a large enough hydrocarbon (**hydrophobic**) component, most organic compounds could fall within this scope. Second, many of the classical lipids (for example, the fatty acids) have significant solubility in water.

A more constricted definition of lipids is to simply classify them as fatty acids and their derivatives, and to treat other hydrocarbon-based natural products separately. **Fatty acids** are carboxylic acids that contain a long, hydrocarbon chain. The derivatives of fatty acids may be acylglycerol esters, wax esters, or alcohols such as sterols. Additional acid derivatives include phosphates (glycerophospholipids) or carbohydrates (glycoglycerolipids).

1.2.1 Hydrocarbons

Comprising a relatively small group of compounds, the least polar organic natural products are the **hydrocarbons** (see plant examples illustrated in Figure 1.1). Hydrocarbons are simply molecules that contain only hydrogen and carbon atoms. The aliphatic hydrocarbons are straight chain hydrocarbons,

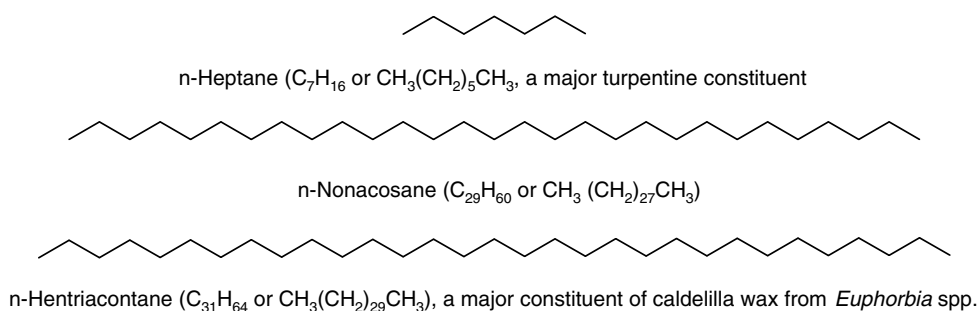


FIGURE 1.1 Some hydrocarbon natural products in plants.

usually having an odd number of carbon atoms, resulting from the decarboxylation of their fatty acid counterparts (Savage et al., 1996). Devoid of any heteroatoms, these compounds have relatively simple structures. Hydrocarbons, in general, may be either **saturated** or **unsaturated** — the latter contain multiple bonds. Each double bond results in two fewer hydrogen atoms relative to the saturated counterpart (thus, four fewer hydrogen atoms for triple bonds) and is, therefore, in a higher oxidation state. They may contain straight chains, branched chains, as well as rings. Being purely organic in nature, they are highly insoluble in water, that is, they are “greasy.” With rare exceptions, such as highly halogenated compounds, they are less dense than water. Compounds containing aromatic rings generally show increased stability. Highly aromatic compounds may have reduced solubility in common organic solvents, due to stronger intermolecular interactions. Note that those highly branched and often cyclic hydrocarbons derived from isoprene can exist as hydrocarbons; however, these materials (terpenes) will be considered separately in Section 1.2.3.

1.2.1.1 Saturated Hydrocarbons

Saturated hydrocarbons are the simplest and least polar organic natural products. **Methane** (CH_4 , sometimes referred to as marsh gas) is an odorless gas that does not occur naturally in plants to any degree. However, it is one of the principal decomposition products, from **methanogens** (methane-producing bacteria). Methane can provide a renewable energy source, something the U.S. Department of Energy, among others, has taken an interest in (Ferry, 1994). Among the gases accumulating in the atmosphere and contributing to the **greenhouse effect** and **global warming**, methane is 21 times as harmful as carbon dioxide, according to the U.S. Environmental Protection Agency (Thorneloe, 1993).

Common hydrocarbon examples, such as hexane, $\text{CH}_3(\text{CH}_2)_4\text{CH}_3$, are not generally found in plants, but rather, are derived from fossilized plant and animal matter. **Turpentine**s, commonly used as paint removers, consist of simple hydrocarbons, particularly **α -** and **β -pinene** as well as ***n*-heptane** $\text{CH}_3(\text{CH}_2)_5\text{CH}_3$, as found in conifers, including the Jeffrey pine (*Pinus jeffreyi*) and the gray pine (*P. sabiniana*). These compounds are produced in resin ducts and are found in blister-like bubbles located along the tree trunks. These are natural insecticides that deter feeding by insect predators, such as bark beetles. The **pitch** from the bubbles found on trunks of white fir (*Abies concolor*) is used by Native Americans to treat burns so as to prevent infection, hasten healing, and reduce pain.

In living plants, saturated hydrocarbons are universally distributed as the waxy coatings (cuticular waxes) on leaves and as **cuticle** waxes on the surfaces of fruits (Hamilton, 1995; Eglinton and Hamilton, 1967). Typical examples include ***n*-nonacosane** $\text{CH}_3(\text{CH}_2)_{27}\text{CH}_3$ and **hentriacontane** $\text{CH}_3(\text{CH}_2)_{29}\text{CH}_3$. Several plants are rich in aliphatic hydrocarbons used in vegetable oils. For example, **olive oil**, derived from the fruits of olive (*Olea europea*), contains hydrocarbons ranging from C_{13} to C_{28} (Dell’Agli and Bosisio, 2002). Branched simple alkanes (again excluding terpenes) rarely occur in significant quantity in plants.

1.2.1.2 Unsaturated Hydrocarbons

The simplest **unsaturated hydrocarbon** is **ethylene**, $\text{H}_2\text{C}=\text{CH}_2$, an important plant hormone (Davies, 2004). **Plant hormones** such as ethylene are small organic compounds that influence physiological

responses at very low concentrations. Produced by the amino acid **methionine**, ethylene causes trees to lose their leaves (**abscission**), stems to thicken, and fruit to ripen. In the latter case, adding low concentrations of ethylene to the air can artificially promote fruit ripening, as with apples (*Malus* spp.) or pineapple (*Ananas comosus*). Concentrations as low as 0.01 ppm were shown to distort the growth of tomato and marigold plants, causing what is termed **epinasty**. Larger unsaturated hydrocarbons are also common as **plant waxes**. Exceptionally high amounts of alkenes were detected in rye (*Secale cereale*) pollen, rose (*Rosa* spp.) petals, and sugarcane (*Saccharum* spp.). As the chain length and degree of unsaturation increase, the hydrocarbons become waxy and then solid at room temperature. Waxes may be either long-chain hydrocarbons or esters of fatty acids.

1.2.1.2.1 Polyacetylenes

Unsaturated natural products can contain not only double bonds but also triple bonds, either in the form of acetylenes or nitriles. The **polyacetylenes** are a unique group of naturally occurring hydrocarbon derivatives characterized by one or more acetylenic groups in their structures (Wu et al., 2004). The electronic arrangement of the carbon atoms in a triple bond results in a linear shape for this region of the molecule. Typical polyacetylenes (see Figure 1.2 for a listing) often contain a wide variety of additional functional groups. The domestic carrot (*Daucus carota*), for example, contains four polyacetylenes, the major one being **falcarinol** (Lund and White, 1990), which is a mild neurotoxin found only to be present in 2 mg·kg⁻¹ (dry weight) of carrot roots. Other plants, such as the water dropwort (*Oenanthe crocata*), are commonly found near streams in the Northern Hemisphere and contain several toxic polyacetylenes and should not be consumed (Hansen and Boll, 1986). The water dropwort (*Oenanthe crocata*) contains the violent toxin, **cicutoxin**, which can result in convulsions and respiratory paralysis (Uwai et al., 2000).

Polyacetylenes have a fairly specific distribution in plant families, existing regularly only in the Campanulaceae, Asteraceae, Araliaceae, Pittosporaceae, and Apiaceae families. Polyacetylenes are also found in the higher fungi, where their typical chain length is from C₈ to C₁₄, whereas the polyacetylenes from higher plants are typically from 14 to 18 carbons in length. Biosynthetically, the polyacetylenes are likely to be derived by enzymatic dehydrogenation from the corresponding olefins. The toxicity of many of the polyacetylenes, including those in the aforementioned water dropwort (*Oenanthe crocata*), as well as fool's parsley (*Aethusa cynapium*), may account for their ability to deter predators in some plants. Similarly, both **wyerone acid** (Nawar and Kutí, 2003) in the broad bean (*Vicia faba*) and **safynol** (Redl et al., 1994) in safflower oil from *Carthamus tinctorius* have been shown to act as natural **phytoalexins**, helping to deter the microorganisms that attack these plants. Several polyacetylenes are shown in Figure 1.2.

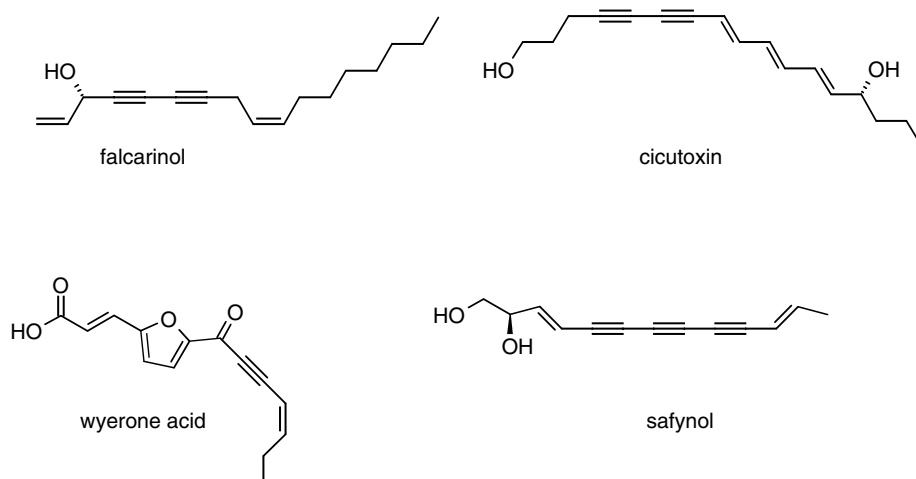


FIGURE 1.2 Some polyacetylenes in plants.

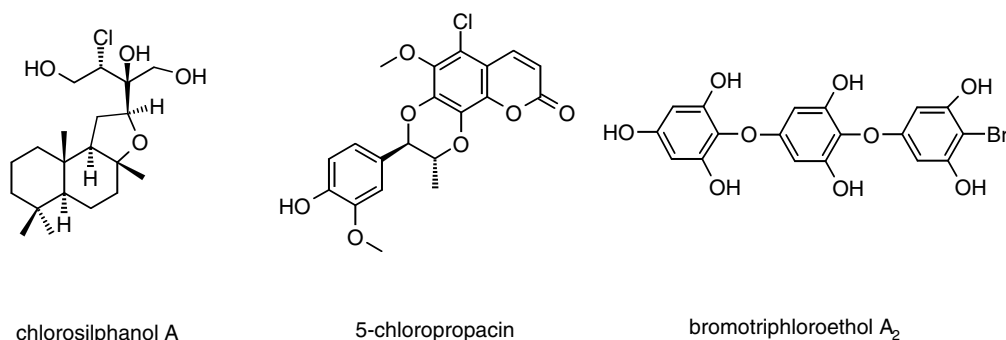


FIGURE 1.3 Halogenated plant natural products.

1.2.2 Functionalized Hydrocarbons

Excluding the lipids and the terpenes, simple **functionalized hydrocarbons** are less abundant but not uncommon in plants. Here, we consider these in ascending order from halide, to alcohol and sulfur-containing hydrocarbons, then to aldehydes and ketones, stopping just before the fatty acids.

1.2.2.1 Halogenated Hydrocarbons (Scheuer, 1973, 1978)

A **halogen** is any of the group 7A elements found on the periodic table of elements (fluorine, chlorine, bromine, iodine, or astatine). Although virtually unknown among their terrestrial counterparts, the marine environment has long been recognized as a source for natural products that contain both chlorine and bromine (Blunt et al., 2004). Iodinated natural products are rare but have been known since the 1970s, and fluorinated natural products were also identified. In the latter case, the source of fluorine in structures such as **nucleocidin** is believed to be derived from fluoroacetyl Co-A (Shaw, 2001). For the other halogens, **haloperoxidases**, such as vanadium bromoperoxidase, are the primary biogenetic source (Butler and Carter-Franklin, 2004). Beginning in the Scheuer laboratories at the University of Hawaii in the 1960s, thousands of different halogenated natural products have since been isolated, often with exotic structures. Examples of halogenated phytochemicals include the chlorinated labdane diterpenoid, **chlorosilphanol A**, from *Silphium perfoliatum* (Pcolinski et al., 1994); the chlorinated coumarin, **5-chloropropacin**, from *Mondia whitei* (Patnam et al., 2005); and the brominated phlorethol, **bromotriphlorethol A₂**, from the brown alga *Cystophora congesta* (Koch and Gregson, 1984), shown in Figure 1.3.

As one example of many, the genus *Laurencia* was found to produce a prodigious assortment of halogenated natural products, several of which are shown in Figure 1.4 (Erickson, 1983). All of these natural products have had their structures confirmed by absolute total synthesis. These include **laurencin** (Irie, Susuki, and Masamune, 1965), **rogiloxepane A** (Guella et al., 1992), **laurallene** (Fukuzawa and Kurosawa, 1979), **prepinnaterpene** (Fukuzawa et al., 1985), **laurencial** (Miyashita et al., 1998), and **kumausallene** (Suzuki et al., 1983).

1.2.2.2 Alcohols

An **alcohol** can be any of a class of compounds characterized by the presence of a hydroxyl group (–OH group) covalently bonded to a saturated carbon atom. Large varieties of volatile aliphatic **alcohols** occur in small concentrations in plants and were classically referred to within the group of **essential oils**. Their role may be related to their often strong odors, attracting them to insect pollinators and animal seed disseminators (see Chapter 2). All of the straight-chain alcohols from C₁ (methanol) to C₁₀ were found in plants in either free or esterified form. Several larger alcohols, such as **ceryl alcohol**, CH₃(CH₂)₂₅OH, are regular constituents of cuticular waxes. Like the terpenes, the aliphatic alcohols, including **cis-3-hexen-1-ol** (leaf alcohol), have characteristic and sometimes attractive odors and are of interest to the fragrance industry (Clark, 1990). The list of alcohols in plants, however, goes on and on, and the reader will notice that the hydroxyl group is associated with many different types of plant molecules.

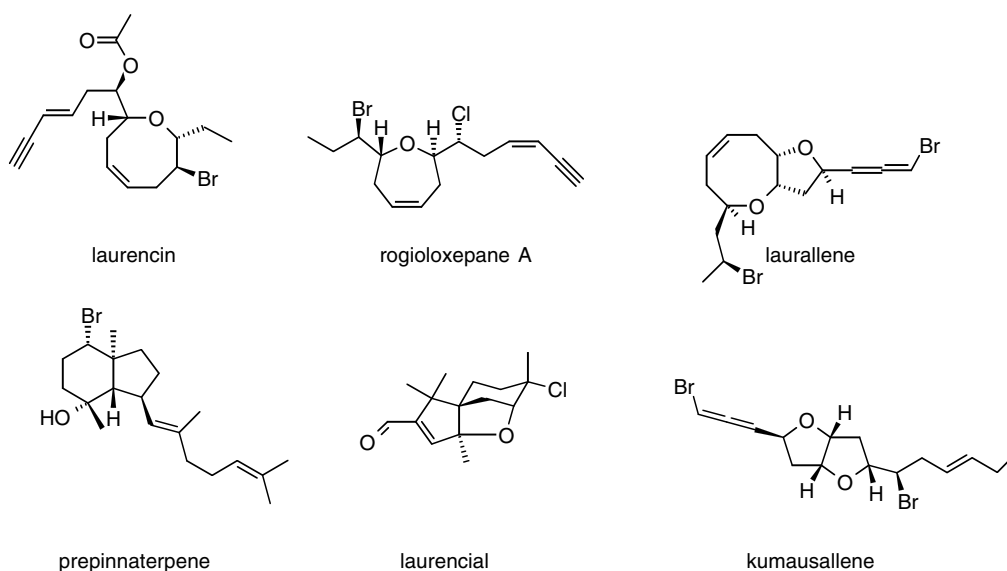


FIGURE 1.4 Halogenated natural products from *Laurencia* species.

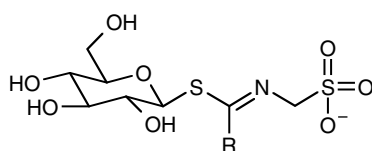


FIGURE 1.5 General structure of glucosinolates.

1.2.2.3 Sulfides and Glucosinolates (Host and Williamson, 2004)

Hydrocarbon **sulfides** have at least one sulfur atom and are found in relatively few plants. Those that contain them, such as skunk cabbage (*Symplocarpus foetidus*), are readily recognizable by their obnoxious odors. Sulfides, including the simple hydrocarbon sulfides, are common among the *Allium* species (onions and their relatives), many of which are **lachrymators** (substances that make the eyes water) and have pungent odors. Cyclic examples, such as thiophenes, are limited primarily to the Asteraceae (aster or sunflower family) and are found in association with the polyacetylenes (Christenson et al., 1990).

The **glucosinolates** are sulfur-containing natural products primarily from the Brassicaceae (mustard family). As shown in Figure 1.5, they consist of a thioglucose and sulfonated oxime, with a specific side chain for each of the over 100 glucosinolates that have been identified (Sørensen, 1990; Rosa et al., 1997).

Some epidemiological data support the possibility that glucosinolate breakdown products derived from *Brassica* vegetables (cabbage, broccoli, and relatives) may protect against human cancers, especially in the gastrointestinal tract and lung (Johnson, 2003).

1.2.2.4 Aldehydes and Ketones

Aldehydes are any of a class of compounds characterized by the presence of a carbonyl group (C=O group) in which the carbon atom is bonded to at least one hydrogen atom. **Ketones**, on the other hand, are compounds where the carbon atom of the carbonyl group is bonded to two other carbon atoms. The citrus fruits, including orange (*Citrus* spp.), lemon (*Citrus limon*), as well as bergamot (*Monarda didyma*), may be cold-pressed to yield terpene-derived essential oils that are rich in aldehyde content, providing them with a unique aroma (Blanco et al., 1995; Lota et al., 2002; Verzera et al., 2003). The aldehyde and ketone components of these oils include **nootkatone**, **citral**, **octanal**, **sinensal** (Moshonas, 1971), and others, as shown in Figure 1.6.

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