

PLANT TERPENES

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Summary

Terpenoids are hydrocarbon natural products based on five-carbon (isoprene) units as their building blocks, numbering more than 30,000 molecules having been discovered to-date. These compounds are classified as to the number of isoprene units, which include the hemiterpenes (1), monoterpenes (2), sesquiterpenes (3), diterpenes (4), sesterterpenes (5), triterpenes (6) and polyterpenes (many units). Of these different major classes of terpenoids, the diterpenes are structurally most diversified, possessing at least 6 large structural groups, within which are more than 20 sub-structural types. The triterpenes are the second largest class, containing two major structural groups and more than 15 sub-structural types. Biologically active compounds are found in each class of the terpenoids, particularly among the sesquiterpenes, diterpenes and triterpenes. In this chapter, chemical descriptions, examples, biosynthetic origin of the various major classes, structural types and sub-types are presented. As far as possible, biological activities of the example of each type or sub-types of terpenes terpenoids are presented. Due to the vast number of different types and sub types, the discussions presented in this chapter, are by necessity, brief. However, the present treatment is meant to stimulate further chemical and biological research, particularly with drug discovery and development being a focal point.

1. Introduction

Terpenes are a large class of natural hydrocarbon secondary metabolites built up from five-carbon isoprene units linked together most commonly in a head-to-tail arrangement, but can be constructed in other configurations with varying degrees of unsaturation, oxidation, functional groups and ring closures, giving rise to a rich diversity of structural classes, with novel skeletons being continuously discovered. These modified hydrocarbons are referred to as terpenoids, which are primarily found to occur in a wide variety of higher plants. They can also be found in some insects and marine organisms. The name, terpene, is derived from the word turpentine, a product of coniferous oleoresins.

The terpenes and terpenoids (terpene like compounds) are classified or grouped according to the number of isoprene units found in the parent nucleus, ranging from one to many. As with any class of compounds, not all terpenoids contain even numbers of intact isoprene units, with a few being degraded isoprene moieties with missing carbons such as the C₁₉ diterpenoids. The simplest type of terpenoids is hemiterpene, consisting of a single 5-carbon isoprene unit (C₅H₈). Their occurrence is rare and is not especially significant biologically. Monoterpenoids are compounds composed of two isoprene units (C₁₀H₁₆) that can be found in acyclic, monocyclic and bicyclic forms, and in various state of oxidation. They can be classified into a number of subclasses based on their cyclic carbon skeletons, with a number of them being biologically and pharmacologically active agents. Sesquiterpenoids are C₁₅ compounds (C₁₅H₂₄) containing three isoprene units, occurring in simple acyclic, simple to macro monocyclic rings, as well as simple and complex bicyclic and tricyclic forms. The structural diversity of sesquiterpenoids is such that the number of carbon skeletons having been reported far exceeds 100. C₂₀ terpenoids are the diterpenoids, which contain four isoprene units (C₂₀H₃₂). Their structural diversity ranges from simple acyclic to complex polycyclic rings. Sesterpenoids are rare C₂₅ (C₂₅H₄₀) compounds. Triterpenoids are C₃₀ compounds (C₃₀H₄₈), numbering more than

4,000 distributed in more than 40 different carbon skeletons, arising from the cyclization of an oxidized form of squalene, the linear parent triterpene. Although not well known as terpenoids, the carotenes are members of the tetraterpenoids (C₄₀H₆₄). Equally not generally thought of as terpenoids are natural rubber, which contains long chains of many *cis* isoprene units, and gutta-percha, which contains many *trans* isoprene units. These natural products are members of the polyterpenoids.

Biosynthetically, the majority of terpenoids are formed via the mevalonic acid (MVA) pathway in plants, but they may also be formed through the methylerythritol 4-phosphate (MEP) pathway. The C₅ isoprene unit, which can be linked together “head to tail” to form linear chains or cyclized to form rings, is considered the building block of the terpenes (terpenoids). Isoprene does not exist *per se*.

Rather, the C₅ unit exists as isopentenyl pyrophosphate (IPP) or its isomer dimethylallyl pyrophosphate (DMAPP) by enzymatic conversion and phosphorylation from mevalonic acid. IPP may be considered as the precursor of the hemiterpenoids. In the biosynthesis of mono- and higher terpenes/terpenoids, the starting molecule is DMAPP, which condenses with an IPP unit to form geranyl pyrophosphate (GPP), leading to the formation of the monoterpenoids. Condensation of GPP with an IPP leads to the formation of farnesyl pyrophosphate (FPP), the precursor of the sesquiterpenoids. FPP + IPP forms geranylgeranyl pyrophosphate (GGPP), the precursor of the diterpenoids. GGPP + IPP leads to the formation of the sesterpenoids. Dimerization of two FPP units gives rise to squalene, which is the precursor of the triterpenes, and indirectly, the steroids. Condensation of appropriate intermediate precursors and/or IPP units leads to tetra- and polyterpenoids.

The biological activity profiles of the terpenoids are diverse and defy simple categorization, with the possible exception of the sesquiterpene lactones, which are well known for being cytotoxic natural products. However, artemisinin, a sesquiterpene lactone endoperoxide, is an important antimalarial drug with high activity against the multidrug-resistant form of *Plasmodium falciparum*. A number of diterpenoids are well known for their biological/pharmacological/therapeutic effects.

Among the bioactive diterpenes are ginkgolides (PAF inhibitors), gibberellins (plant growth hormones), phorbol esters (tumor promoters), and the anti-cancer agent, paclitaxel. Members of the triterpenoids are biologically active, among which are the ginsenosides (adaptogens), betulinic acid (anti-melanoma), brusatol (chemopreventive), and boswellic acids (anti-inflammatory and anti-arthritic). As cited in the sections to follow, many other terpenoids possess interesting and diverse biological activities and therapeutic potentials, biological tools or lead compounds for drug discovery research.

Chemical and biological studies have shown that the terpenoids possess a variety of chemical, physical and biological activities. Because of their vast numbers (more than 30,000) and their different physical, chemical and biological properties, it is not possible to provide a comprehensive treatise on all of the different groups of terpenoids in this chapter. Rather, a select number of the largest and most commonly encountered groups of terpenoids, will be discussed from the chemical and biological perspective in the following sections.

2. Hemiterpenes

Hemiterpenes are the simplest terpenes. The number of known hemiterpene aglycones is less than 100. Most of them occur as oils, and mostly water insoluble, but some sugar containing molecules are water soluble. These compounds can be found in different plant parts. The best known hemiterpene is isoprene, which is the basic unit of all terpenes. Tiglic, angelic and isovaleric acids are examples of well known naturally occurred hemiterpenes found in plants (Figure 1). Recently, the chlorinated hemiterpenes utililactone and epiutililactone were found in the leaves of *Prinsepia utilis* and the anti-platelet aggregation active compound pubescenoside A was reported from *Ilex pubescens*.

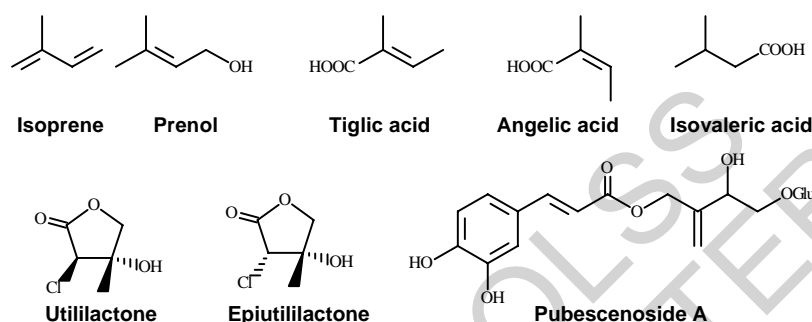


Figure 1. Representative hemiterpenes

3. Monoterpenes

Monoterpenes (10 carbons of two condensed isoprene units) are extensively distributed in secretory tissues such as oil glands or chambers and resin canals of higher plants, insects, fungi and marine organisms. Monoterpenes are major constituents of plant volatile or essential oils. A number of monoterpenes are oxygenated, and many exhibit biological activities and fragrance, and are often used as medicinal agents or ingredients in cosmetics. When monoterpenes occur in glycosidic form or are substituted with polyhydroxyl or other heavy atom groups, their volatile property is lost.

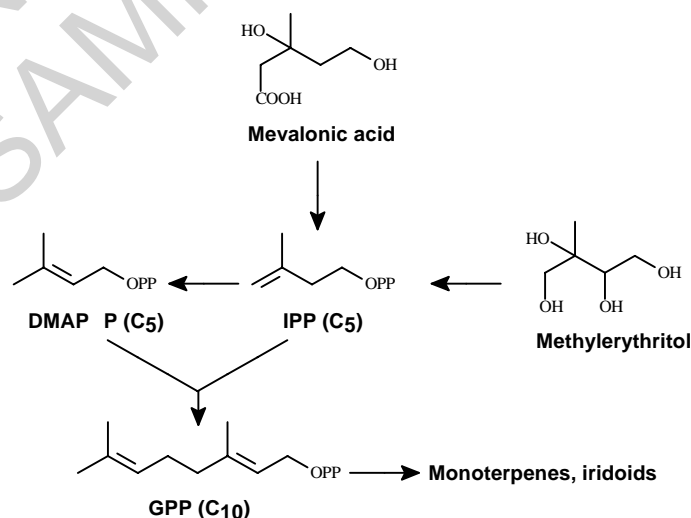


Figure 2. Mevalonic acid methylerythritol biosynthetic pathways of monoterpenes.

The monoterpenoids may be biosynthesized *via* either the mevalonic acid or methylerythritol pathway. Either phosphorylated mevalonic acid or methylerythritol forms isopentenyl pyrophosphate (IPP), which is further isomerized to dimethylallyl pyrophosphate (DMAPP). These two C₅ active isopentene units, IPP and DMAPP, are condensed head to tail to produce geranyl diphosphate (GPP) by *trans* 1, 2-addition and elimination. GPP is further transformed in living organisms to produce various basic skeletons of monoterpene groups (Figure 2).

Monoterpenoids occur in more than 30 different known carbon skeletons. Among them, approximately 20 are common and can be divided into acyclic, monocyclic and bicyclic types (Figure 3). The acyclic monoterpenes can be regarded as derivatives of 2, 6-dimethyloctanes with linalool and citronellol being examples (Figure 4). Monocyclic monoterpenes have more than ten different skeletal variations, with menthol as an important representative. Bicyclic monoterpenes possess many carbon skeletons, with thujane, camphane, carane, pinane, isocamphane, and fenchane being the common types. The former four structure types can be regarded as derivatives of menthane, extensively distributed in members of the Pinaceae and Cupressaceae families.

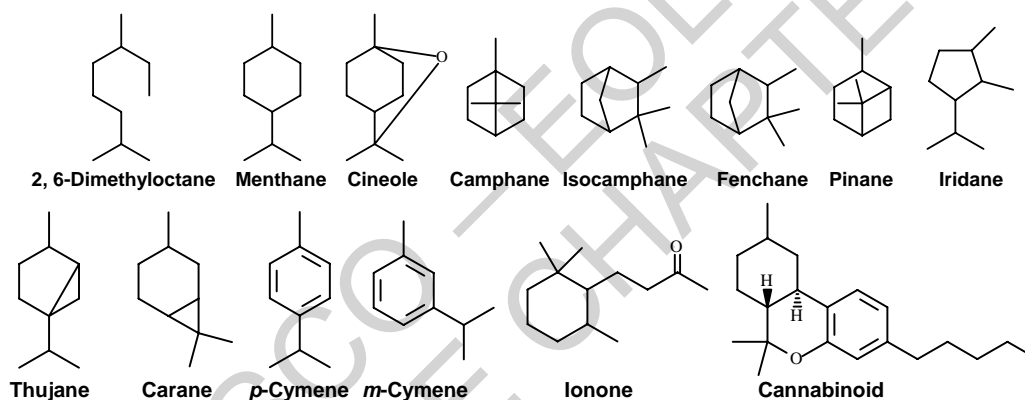
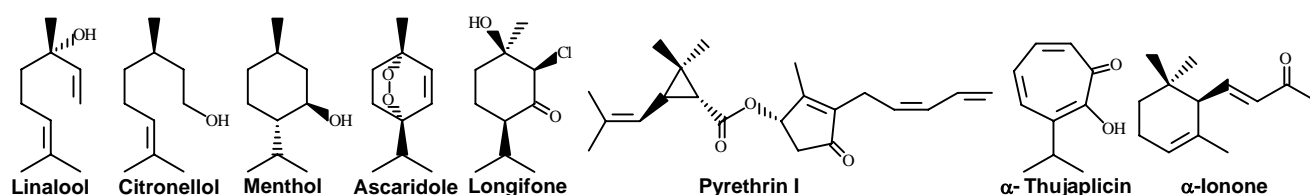


Figure 3. Common monoterpene skeletons

A number of structurally unique peroxy containing monoterpenoids have been isolated from plants and marine organisms. For example, ascaridole, a naturally occurring organic peroxide, has been found as a constituent of a number of plant species.

Another unusual group of monoterpenoids are the chlorine-containing C₁₀ compounds, which are primarily found in marine organisms. Although very rarely found in terrestrial plants, they are, however, not unknown. For example, longifone (Figure 4) is a chlorine-containing monoterpene isolated from *Mentha longifolia* (Lamiaceae).



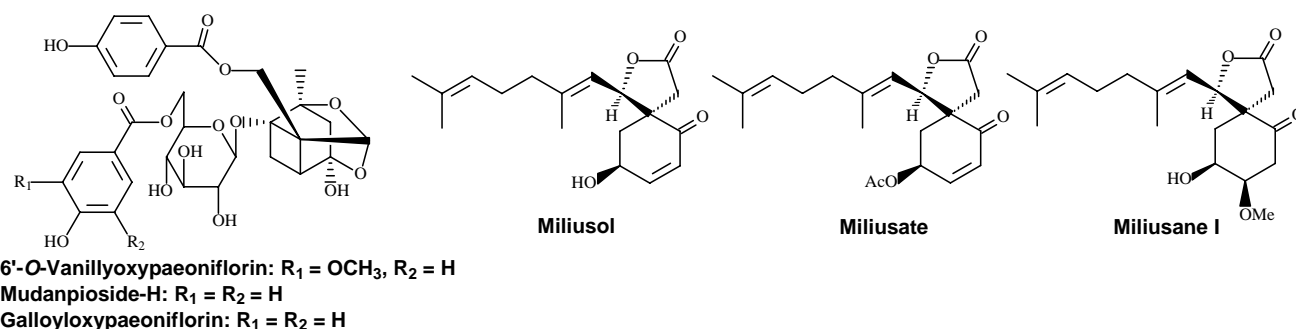


Figure 4. Representative monoterpenoids

Although monoterpenes are biosynthesized *via* the mevalonic acid or methylerythritol pathways, it has been demonstrated that some monoterpenoids can be formed by the glyceraldehyde-3-phosphate and pyruvate route. These compounds are referred to as “irregular monoterpenes” and are found concentrated in the family Asteraceae. Representatives of this group of “terpenoids” include the pyrethrins (e.g. pyrethrin I), trononoides (α -thujaplicin) and ionones (α -ionone) (Figure 4).

Biologically, the monoterpenes have been found to possess a variety of biological effects, including antibacterial, sedative, antitumor, cytotoxic, anti-inflammatory, insecticidal, molluscicidal and others. They have historically been important ingredients individually or as constituents of volatile (essential) oils in medicinal and economic products including cosmetics and other fragrant products. One of the best known and most often used monoterpenes is menthol (Figure 4), which has been used as a topical antipruritic, a counterirritant in external analgesic preparations, as antiseptic and as a flavoring agent in chewing gums, toothpaste and tobacco products such as cigarettes. In drug discovery research reports, linalool, a monoterpene alcohol found in the essential oils from many aromatic plants was determined to be able to moderately inhibit cell proliferation. Subtoxic concentrations of linalool potentiated doxorubicin-induced cytotoxicity and pro-apoptotic effects in two human breast adenocarcinoma cell lines, MCF-7 WT and multidrug resistant MCF-7 AdrR. It may improve the therapeutic index of anthracyclines in the management of breast cancer, especially in MDR tumors. The monoterpene glycosides, 6'-O-vanillyloxypaeoniflorin, mudanpioside-H and galloyloxypaeoniflorin, isolated from the root bark of *Paeonia suffruticosa*, a traditional Chinese medicine, showed antibacterial activities against a host of pathogens capable of zoonosis. In a recent study, a new class of monoterpenes with a skeleton of homogentisic acid-coupled to geranene, designated as miltusanes, was isolated from *Milium sinensis*. A number of the miltusanes such as miliusol, miliusate and miliusane I (Figure 4) demonstrated potent cytotoxic activity against a panel of cancer cell lines. Horticulturally, the pyrethrins (Figure 4) from *Pyrethrum cinerariaefolium* flowers have been used as potent natural insecticides.

Iridoids, belonging to the iridane skeleton, represent a large group of natural monoterpeneoid compounds, which are widely distributed in sympetalous plants within the dicotyledons and a variety of animal species. In general, the number of carbons in the iridoid is, but some are reduced to nine and on very rare occasions, eight carbons. Although they exist in both free and binding forms, most iridoids occur as glucosides, and

are further classified into iridoids (e.g. lamiridosins A/B and genipin) or as *seco*-iridoids (e.g. gentiopicroside) (Figure 5). They serve as important chemotaxonomic markers and many are bioactive agents. In a recent study, a group of iridoids were discovered to have anti-hepatitic C virus (HCV) activity. The study found that only the iridoid aglycones such as lamiridosins A/B and genipin were active against HCV, and their corresponding glycosides such as lamalbid and geniposide showed no activity against HCV.

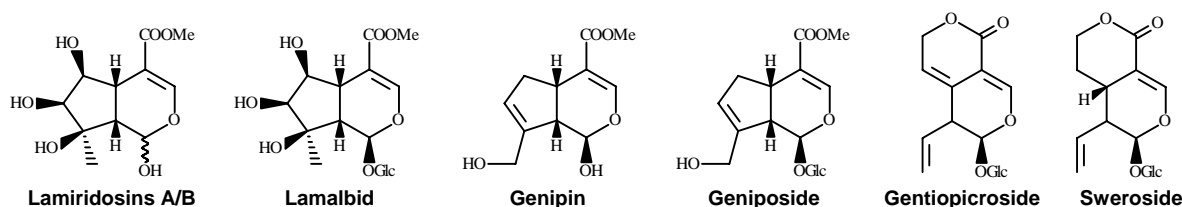


Figure 5. Representative iridoids

In recent years, much progress has been made on the synthesis, biotransformation, biogenesis, isolation, structure determination and bioactivity studies of monoterpenoids. As research on this class of compounds continues, it is anticipated that many novel monoterpenoids including heretofore unknown carbon skeleton and/or biological activity will be discovered from terrestrial plants, animals and marine organisms.

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Biographical Sketches

Hongjie Zhang obtained his BS in chemistry in the Department of Chemistry, Yunnan University, Kunming, Yunnan, China, 1985, and his MS (1988) and Ph.D. (1994) in phytochemistry, Kunming Institute of Botany (KIB), the Chinese Academy of Sciences, Kunming, Yunnan, China.

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