



NATURE & NUTRITION

A New Era of Therapeutic Herbs



Preface

Plants have been well documented for their medicinal uses for thousands of years and traditional medicines are still a major part of habitual treatments of different maladies in different parts of the world. In recent years, there has been growing interest in alternative therapies and the therapeutic use of natural products, especially those derived from plants. Plants are considered as one of the main sources of biologically active materials. Phytochemical screening of medicinal plants has contributed a great deal for the discovery of new drugs. Despite technological developments, herbal drugs still occupy a preferential place in a majority of the population in the Third World and terminal patients in the West. Herbal drugs, in addition to being cost effective and easily accessible, have been used since time immemorial and have passed the test of time without having any side effects. The multitarget effects of herbs (holistic approaches) are the fundamental basis of their utilization. This approach is already used in traditional systems of medicine like Ayurveda, which has become more popular in the West in recent years. However, the integration of modern science with traditional uses of herbal drugs is of the utmost importance if ones wishes to use ancient knowledge for the betterment of humanity.

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Abstract

The use of herbal medicinal products and supplements has increased tremendously over the past three decades with not less than 80% of people worldwide relying on them for some part of primary healthcare. This past decade has obviously witnessed a tremendous surge in acceptance and public interest in natural therapies both in developing and developed countries, with these herbal remedies being available not only in drug stores, but now also in food stores and supermarkets. The use of herbal remedies has also been widely embraced in many developed countries with complementary and alternative medicines (CAMs) now becoming mainstream in the UK and the rest of Europe, as well as in North America and Australia. In the developed countries, the most important among many other reasons for seeking herbal therapy is the belief that it will promote healthier living. Herbal medicines are, therefore, often viewed as a balanced and moderate approach to healing and individuals who use them as home remedies and over-the-counter drugs spend huge amount of money (in excess of billions of dollars) on herbal products. As the global use of herbal medicinal products continues to grow and many more new products are introduced into the market, public health issues, and concerns surrounding their safety are also increasingly recognized. Although some herbal medicines have promising potential and are widely used, many of them remain untested and their use also not monitored. This makes knowledge of their potential adverse effects very limited and identification of the safest and most effective therapies as well as the promotion of their rational use more difficult. It is also common knowledge that the safety of most herbal products is further compromised by lack of suitable quality controls, inadequate labeling, and the absence of appropriate patient information. It has become essential, therefore, to furnish the general public including healthcare professionals with adequate information to facilitate better understanding of the risks associated with the use of these products and to ensure that all medicines are safe and of suitable quality.

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Chapter 1.

Plant Secondary Metabolites

1. Introduction

Secondary metabolites are organic molecules that are not involved in the normal growth and development of an organism. While primary metabolites have a key role in survive of the species, playing an active function in the photosynthesis and respiration, absence of secondary metabolites does not result in immediate death, but rather in long-term impairment of the organism's survivability, often playing an important role in plant defense. These compounds are an extremely diverse group of natural products synthesized by plants, fungi, bacteria, algae, and animals. Most of secondary metabolites, such as terpenes, phenolic compounds and alkaloids are classified based on their biosynthetic origin. Different classes of these compounds are often associated to a narrow set of species within a phylogenetic group and constitute the bioactive compound in several medicinal, aromatic, colorant, and spice plants and/or functional foods. Secondary metabolites are frequently produced at highest levels during a transition from active growth to stationary phase. The producer organism can grow in the absence of their synthesis, suggesting that secondary metabolism is not essential, at least for short term survival. A second view proposes that the genes involved in secondary metabolism provide a “genetic playing field” that allows mutation and natural selection to fix new beneficial traits via evolution. A third view characterizes secondary metabolism as an integral part of cellular metabolism and biology; it relies on primary metabolism to supply the required enzymes, energy, substrates and cellular machinery and contributes to the long-term survival of the producer. A simple classification of secondary metabolites includes tree main groups: terpenes (such as plant volatiles, cardiac

glycosides, carotenoids and sterols), phenolics (such as phenolic acids, coumarins, lignans, stilbenes, flavonoids, tannins and lignin) and nitrogen containing compounds (such as alkaloids and glucosinolates). A number of traditional separation techniques with various solvent systems and spray reagents, have been described as having the ability to separate and identify secondary metabolites.

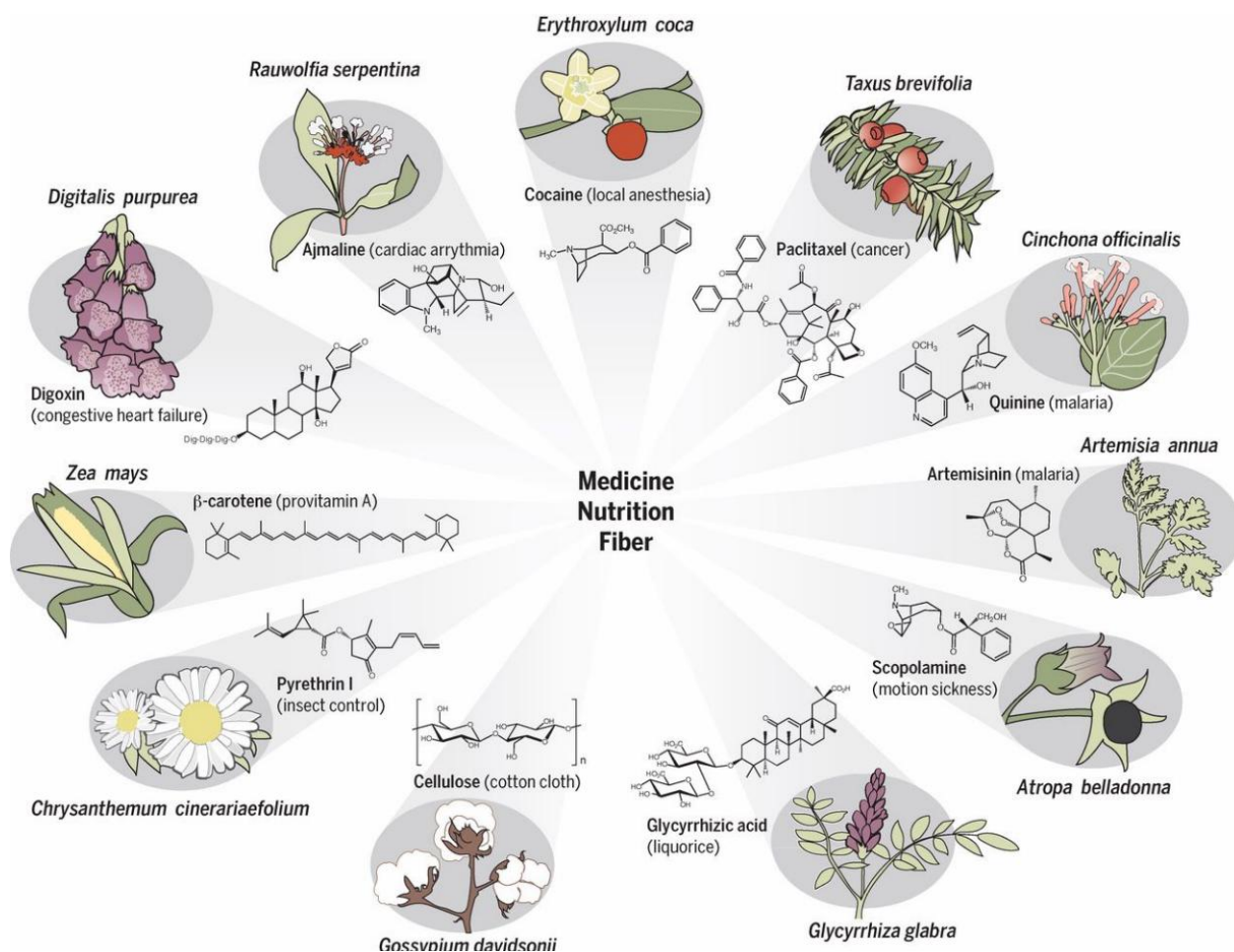


Figure 1. Selected plants and their uses [1]. Throughout history, plants have served as sources of a plethora of chemicals that provide humankind with medicine, fiber, and nutrition. The chemical diversity of plants is enormous. Plants evolved the biosynthesis of a cornucopia of novel chemicals to survive and communicate in a complex ecological environment. Although some plant chemicals are sharp or bitter tasting (glucosinolates and pyrrolizidine alkaloids) to deter herbivory, others such as anthocyanins and carotenoids are brightly colored flower pigments that attract pollinators. Chemicals that are cytotoxic or otherwise physiologically active in mammals are used, for example, as pain-killers, chemotherapeutics, and other drugs. All of these plant chemicals are made through species-specific, specialized biochemical pathways that modify metabolites of primary metabolism. A plethora of new chemicals and metabolic pathways are likely hidden in plant genomes awaiting discovery. Although structures for 200,000 natural products are known, only 15% of the estimated 350,000 plant species have been investigated for their chemical constituents.

2. Terpenoids

Terpenoids (isoprenoids) encompass more than 40 000 structures and form the largest class of all known plant metabolites. Some terpenoids have well-characterized physiological functions that are common to most plant species. In addition, many of the structurally diverse plant terpenoids may function in taxonomically more discrete, specialized interactions with other organisms.

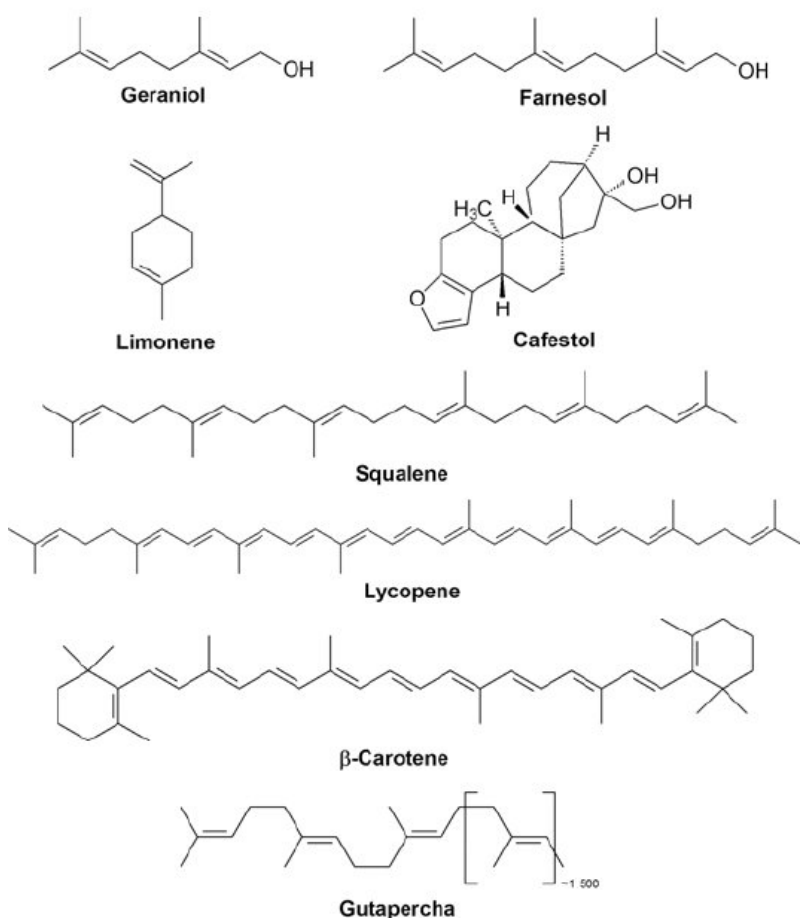
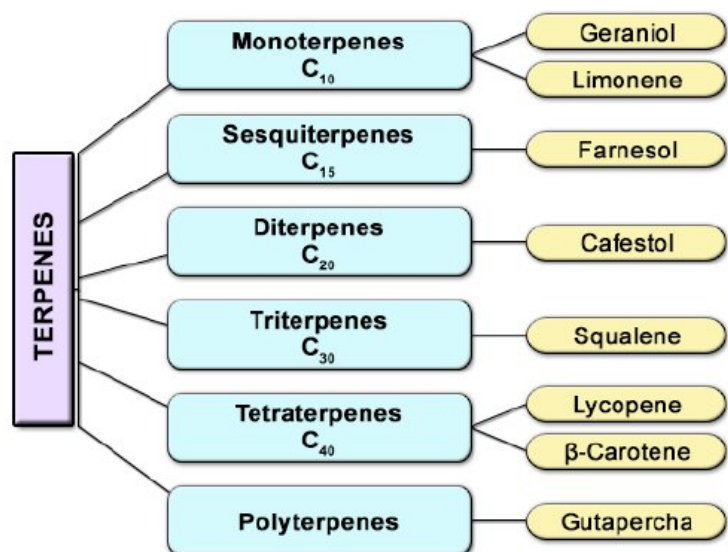


Figure 2. Important carotenoids discovered so far.

Historically, specialized terpenoids, together with alkaloids and many of the phenolics, have been referred to as secondary metabolites. More recently, these compounds have become widely

recognized, conceptually and/or empirically, for their essential ecological functions in plant biology.

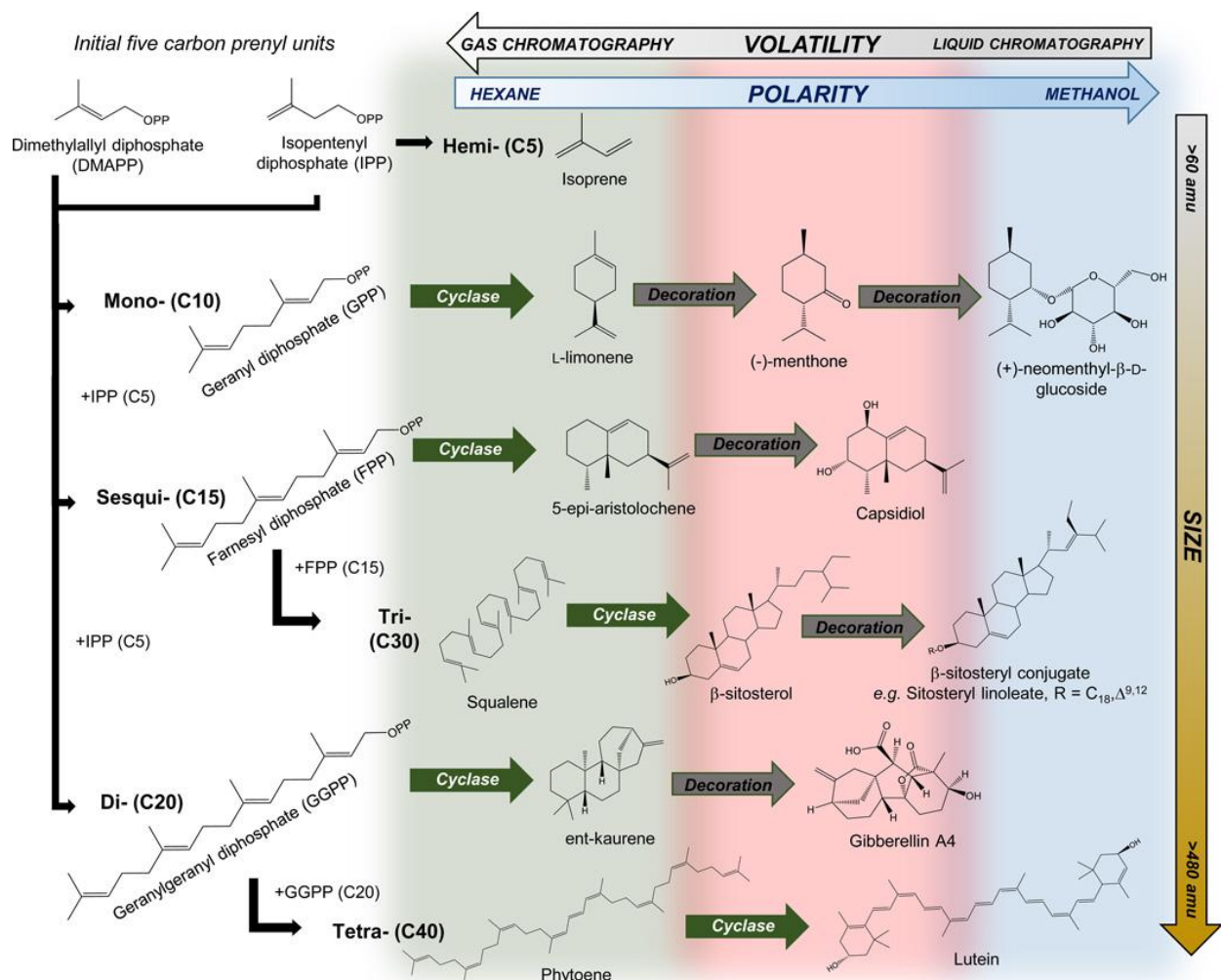


Figure 3. A schematic depiction of terpene metabolism emphasizing the biosynthesis of the different classes of compounds and their physical properties (volatility and polarity) [4]. DMAPP and IPP are the basic building blocks used to generate the allylic diphosphate precursors specific to each terpene class: GPP for monoterpenes; FPP for sesquiterpenes and triterpenes; and GGPP for diterpenes and tetraterpenes. Ionization of the phosphorylated precursors yields linear hydrocarbon forms, while the coupled ionization/cyclization reactions catalyzed by synthases/cyclases yield an incredibly rich array of cyclized hydrocarbons. These linear and cyclized hydrocarbon scaffolds are generally nonpolar or mono-hydroxylated, and their volatility is correlated with their molecular mass. The smaller the compound, the more volatile they will be. But all these terpene scaffolds are also subject to additional layers of modification including hydroxylations, glycosylations, acylations, and aroylations, which alter the physical size and nature of the terpene molecule, and can increase their polarity. This figure is also color coded in reference to the protocols discussed here which might be the most efficient for extraction, quantitation and structural identification of the individual terpene molecules. Protocol 1 is designed for largely nonpolar compounds and is highlighted in green; Protocol 2 is for those molecules having a more polar nature (red); and those terpenes having the greatest polarity are probably best extracted, quantified and qualified by Protocol 3 (blue).

Owing to their diverse biological activities and their diverse physical and chemical properties, terpenoid plant chemicals have been exploited by humans as traditional biomaterials in the form

of complex mixtures or in the form of more or less pure compounds since ancient times. Plant terpenoids are widely used as industrially relevant chemicals, including many pharmaceuticals, flavors, fragrances, pesticides, and as large-volume feedstocks for chemical industries [2,3].

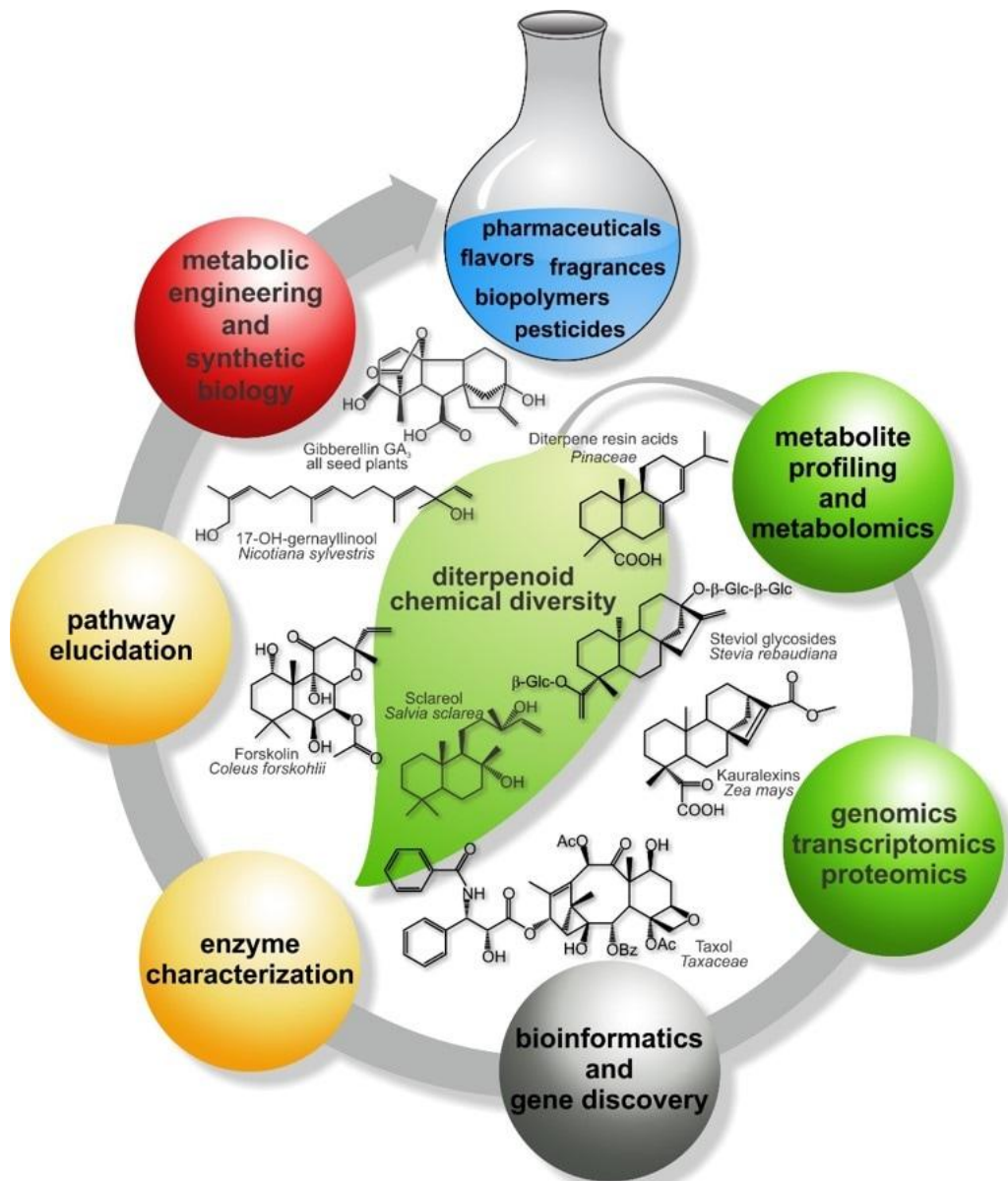


Figure 4. Functional genomics enable efficient discovery of terpenoid metabolic pathways [12]. In order to investigate and ultimately harness the vast chemical repertoire of plant terpenoid metabolism, a core strength of our lab is the efficient identification of terpenoid-metabolic genes, enzymes and pathways by combining genomics-enabled gene discovery using in-house protein databases, rapid enzyme biochemical characterization through microbial and plant co-expression assays, and de novo identification of novel metabolites using mass spectrometry and NMR approaches. Using these tools, we have identified more than 50 functionally distinct TPS and P450 enzymes in over a dozen plant species with relevance for food, bioenergy and medicine. We integrate these biochemical insights with in planta terpenoid profiling via GC- and LC-MS analyses, genetic gene function studies

using CRISPR/Cas9-enabled pathway alteration, as well as plant-environment interaction studies using in vitro and in vivo plant-pathogen and plant-microbiome analyses to investigate the bioactivity of terpenoid metabolites and evaluate their potential for agricultural and other biotechnology applications.

2.1 Monoterpenes and sesquiterpenes (Plant volatiles)

As nouns the difference between sesquiterpene and monoterpene is that sesquiterpene is (chemistry) any terpene formed from three isoprene units, and having fifteen carbon atoms; includes several plant pigments such as the flavones while monoterpene is (organic chemistry) any terpene formed from two isoprene units, and having ten carbon atoms; either hydrocarbons such as pinene, or compounds with functional groups such as camphor [5]. Monoterpenes evaporate easily and have a low boiling point. Monoterpenes are mostly colorless and odorless, prone to oxidation. Oxidants from monoterpenes could be irritant. Monoterpenes are antiseptic, antiviral and bactericidal [6].

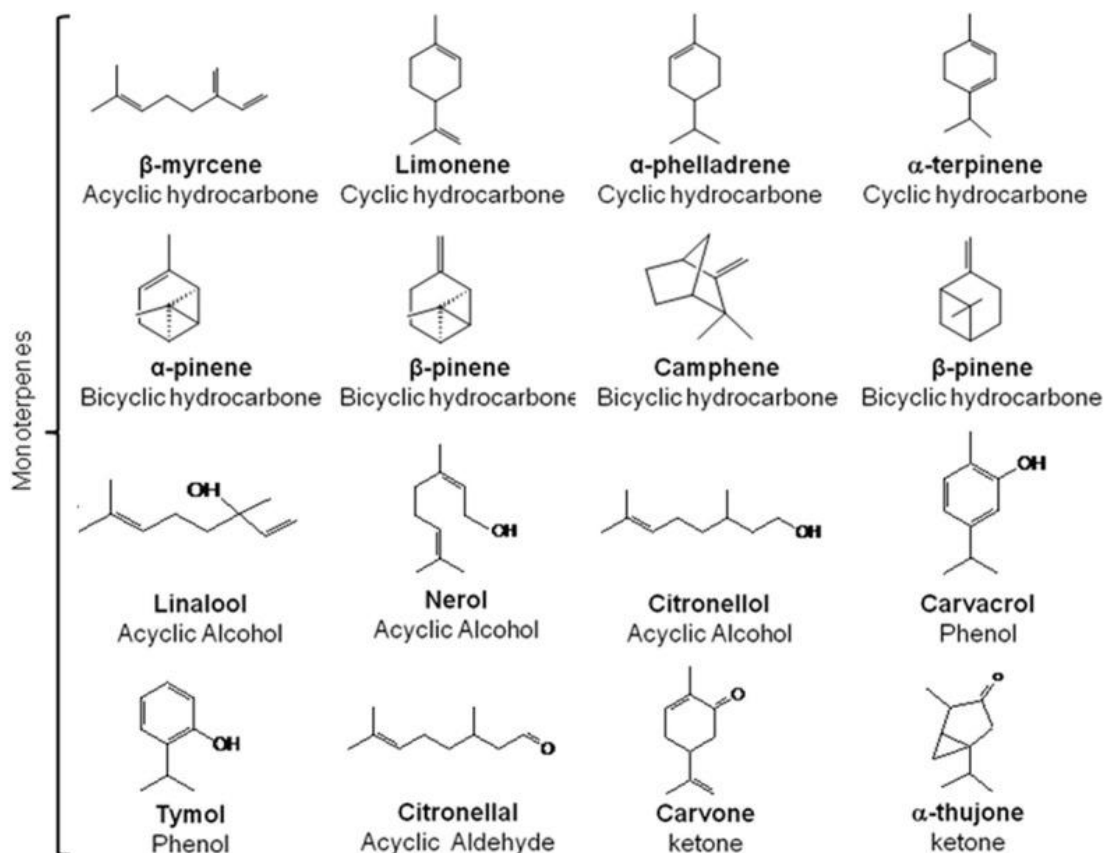


Figure 5. Examples of some mono-terpenes compounds found in essential oils of plants [7].

Plant-derived essential oils containing monoterpenoids have been used as antifungal drugs since ancient times, depending both on application method and dose manner. Studies on the antimicrobial activity of essential oils from aromatic species used in Brazil shows that the oils present one or more active fraction, being monoterpenes the major constituents. The monoterpenes citral, citronellal, L-carvone, isopullegol and α -pinene were diluted in ethanol to

final concentrations from 0.2 to 1%. All monoterpenes were found to inhibit the growth of the three studies fungi in a dose-dependent manner [8].

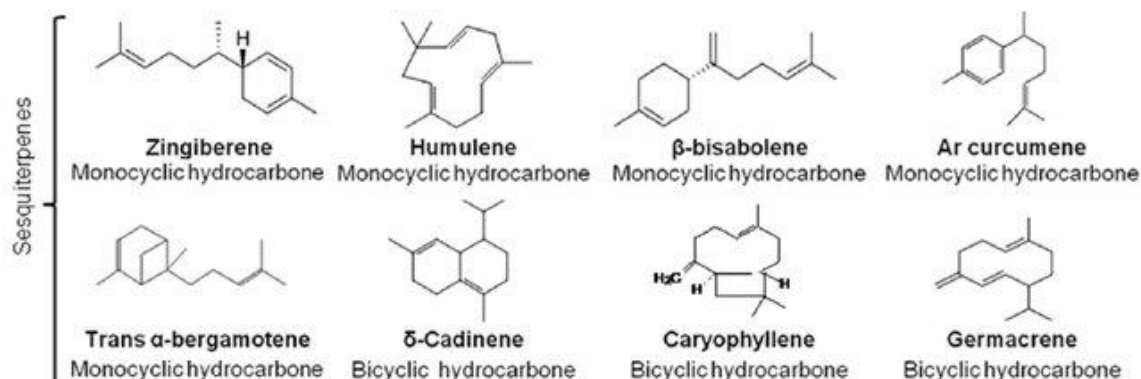


Figure 6. Examples of some sesquiterpenes compounds found in essential oils of plants [7].

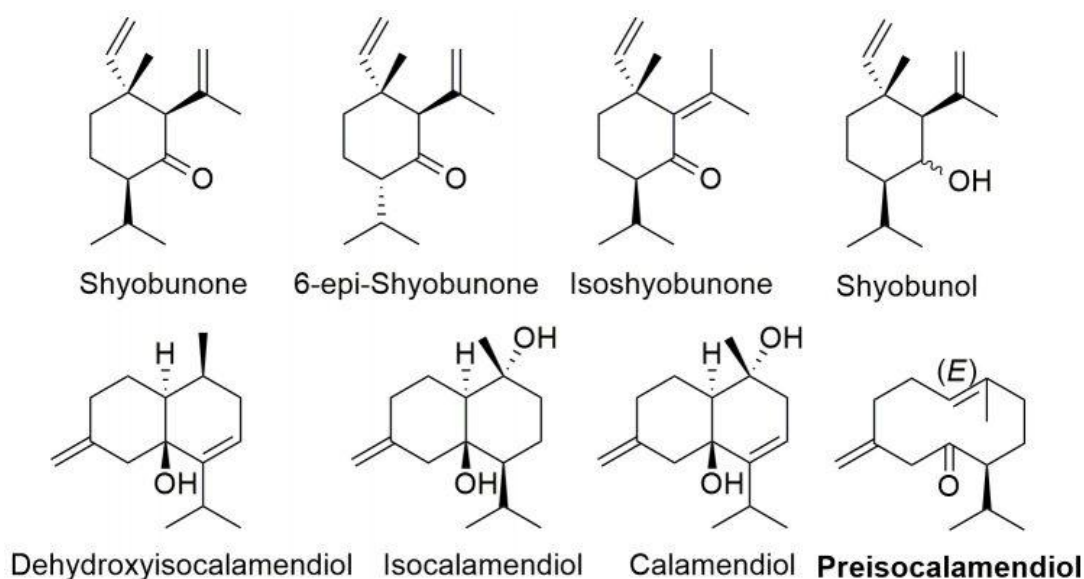


Figure 7. Structures of the uncommon oxygenated sesquiterpenes observed in Bolivian *Schinus molle* essential oils [8].

Sesquiterpenes are less volatile than terpenes, have a greater potential for stereochemical diversity and have stronger odors. They are anti-inflammatory and have bactericidal properties. Sesquiterpenes oxidize over time into sesquiterpenols. In patchouli oil, this oxidation is thought to improve the odor. Sesquiterpenes can be monocyclic, bicyclic or tricyclic and are a very diverse group. When sesquiterpenes occur in essential oils it is mostly in combination with monoterpenes. Sesquiterpenes have a higher melting point than monoterpenes. Sesquiterpenes are anesthetic, antifungal, antiseptic and antibacterial [9-11]. Sesquiterpenes are less volatile than terpenes, have a greater potential for stereochemical diversity and have stronger odors. They are anti-inflammatory and have bactericidal properties. Sesquiterpenes oxidize over time into sesquiterpenols. In patchouli oil, this oxidation is thought to improve the odor [10]. Like

monoterpenes, sesquiterpenes may be acyclic or contain rings, including many unique combinations. Biochemical modifications such as oxidation or rearrangement produce the related sesquiterpenoids. Sesquiterpenes are found naturally in plants and insects, as semiochemicals, e.g. defensive agents or pheromones [23]. Sesquiterpenes are colorless lipophilic compounds. Biosynthesis in plants is from three isoprene units, and occurs via farnesyl pyrophosphate (FPP), in the endoplasmic reticulum. Sesquiterpenes consist of a 15-carbon backbone, and whilst diverse in their structure, the majority, and the most functional forms are cyclic, and consequently the focus of this review will rest upon these compounds. The large number of sesquiterpene synthases coupled with the fact that a single synthase may produce numerous products and further modifications after sesquiterpene synthesis, such as oxidation and glycosylation take place result in a vast number of varied structures, many similar synthases may produce the same products, in different ratios which affect the metabolite profile of a plant and can be used to classify closely related species or subspecies [24].

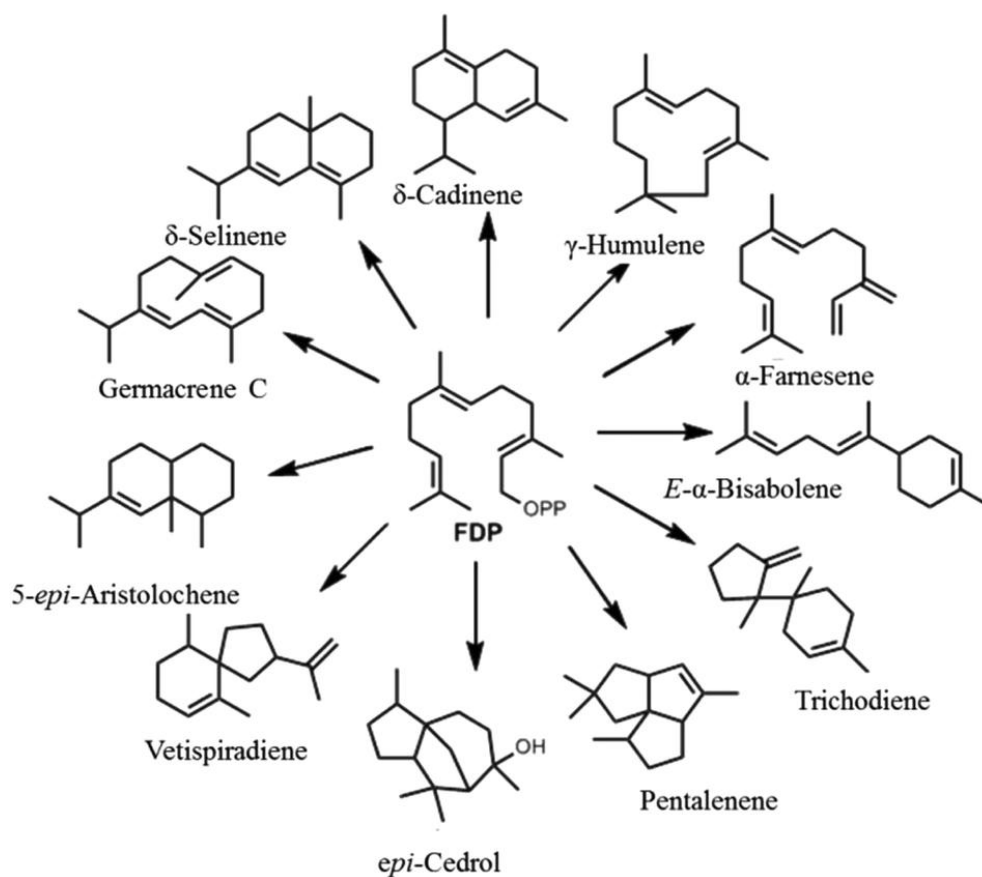


Figure 8. Representative figure of multiproduct terpene synthases converting a single substrate (FDP) into a bouquet of cyclic and acyclic products [13].

Biological Activities: Studies in recent decades have demonstrated that terpenes exert anti-inflammatory effects by inhibiting various proinflammatory pathways in ear edema, bronchitis, chronic obstructive pulmonary disease, skin inflammation, and osteoarthritis. Terpenes have been shown to exert anti-tumorigenic effects against such processes in a number of in vivo and

in vitro systems, thus suggesting their potential uses as chemotherapeutic agents for treating tumors. Numerous studies have shown that essential oils derived from various plants have neuroprotective effects against neurodegenerative conditions in vivo and in vitro. Therefore, as a main component of plant essential oils, terpenes may be beneficial to human neuronal health. However, only few studies have focused on the beneficial effects of terpene components of plant essential oils on neuronal health [14,15]. Antimicrobial and antioxidant properties of essential oils are of great interest in food, cosmetic and pharmaceutical industries since their possible use as natural additives emerged from the tendency to replace synthetic preservatives with natural ones [16]. However, due to the large number of components and synergistic or antagonistic interactions among them, it is possible that essential oils have cellular targets other than cell membranes [17]. Studies into the health benefits of sesquiterpene lactones tend to focus on their anti-tumor potential as some of the SLs have been found to show enough potential to enter clinical trials. Fewer papers look at other applications in disease treatment, and at prospective health benefits. Despite this, work shows that there is much potential for sesquiterpene lactones in the treatment of cardiovascular diseases and their use as antimalarials and are responsible for a range of other effects such as prevention of neurodegeneration, antimigraine activity, analgesic and sedative activities and treatment of ailments such as diarrhea, flu, and burns. The cardiovascular effects are the result of their ability to relax smooth muscle tissue by inhibiting iNOS up-regulation, and consequently increasing levels of NO. The cause of this effect is widely believed to be due to inhibition of NF- κ B. In addition, some sesquiterpene lactones protect the gastric lining from ulcer development, another consideration is that parthenolide, the principle component in feverfew and its derived medicines, has been one of the most commonly used sesquiterpenoids, to the exclusion of other compounds [24].

Toxicity Issues: Most of these terpenes easily enter the human body by oral absorption, penetration through the skin, or inhalation leading to measurable blood concentrations. Several studies showed that some monoterpenes (e.g., pulegone, menthofuran, camphor, and limonene) and sesquiterpenes (e.g., zederone, germacrone) exhibited liver toxicity, which is mainly based on reactive metabolites formation, increased concentration of reactive oxygen species and impaired antioxidant defense. There is a high probability that many other terpenes, without sufficiently known metabolism and effects in human liver, could also exert hepatotoxicity. Especially terpenes, that are important components of essential oils with proved hepatotoxicity, should deserve more attention. Intensive research in terpenes metabolism and toxicity represent the only way to reduce the risk of liver injury induced by essential oils and other terpenes-containing products [18]. Sesquiterpene lactones (STLs)-containing plants have long been known to induce a contact dermatitis in exposed farm workers, and also to cause several toxic syndromes in farm animals. More recently, concerns are been raised regarding the genotoxic potential of these compounds and the embryotoxicity of artemisinins. A growing number of STLs are being reported to be mutagenic in different in vitro and in vivo assays [25].

2.2. Diterpenes and sesterterpenes

Diterpenes are the most important plant metabolites that are derived from geranyl geranyl pyrophosphate (GGPP) and are classified into several categories, namely phytanes, labdanes, halimane, clerodanes, pimaranes, abietanes, cassanes, rosanes, vouacapanes, podocarpanes,

trachlobanes, kauranes, aphidicolanes, stemodanes, stemaranes, bayeranes, atisanes, gibberellanes, taxanes, cembranes, daphnanes, tiglianes, and ingenanes classes.

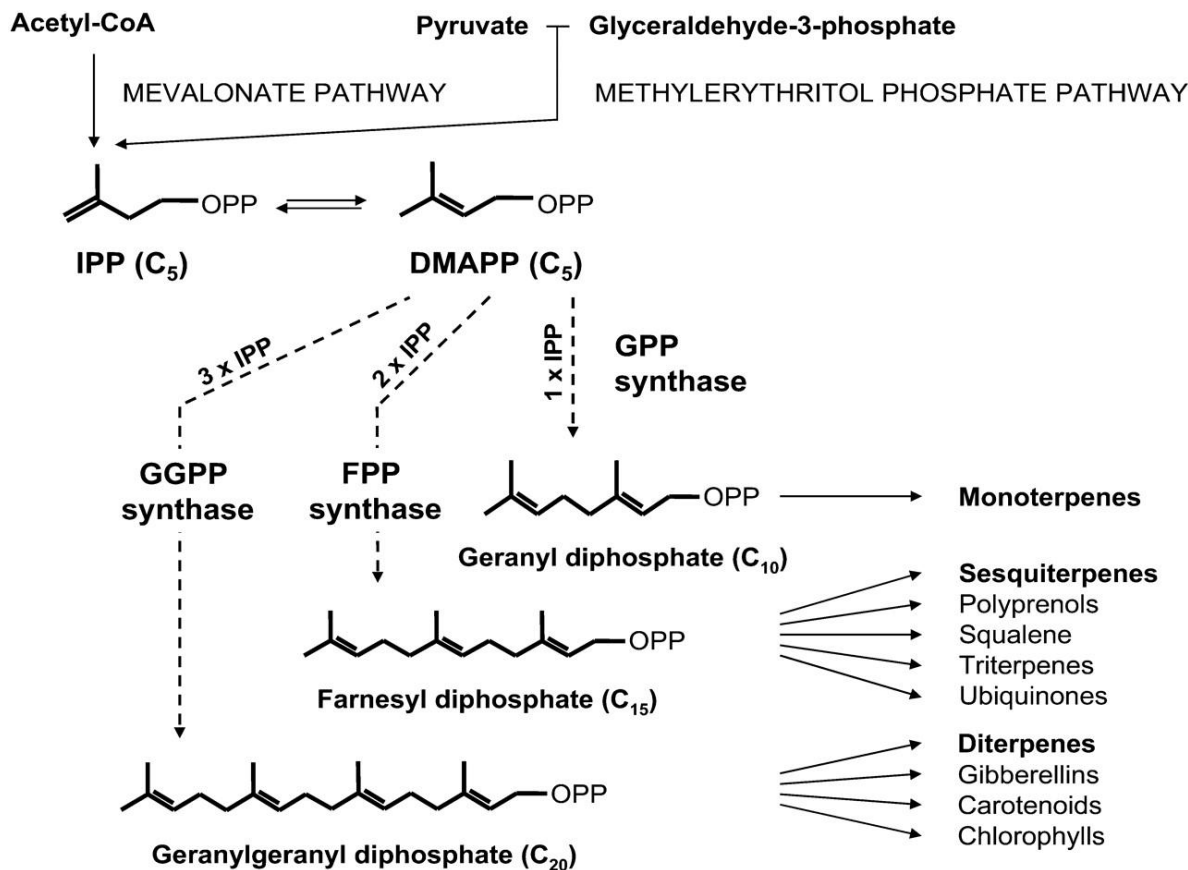


Figure 9. Outline of terpenoid biosynthesis leading to the major conifer oleoresin components, monoterpenes and diterpenes, as well as to other classes of terpenes or compounds with terpene components [19]. In the first phase of terpenoid biosynthesis, IPP and DMAPP are formed via the plastidial methylerythritol phosphate pathway and the cytosolic mevalonate pathway. The next phase consists of the reactions catalyzed by short-chain IDSs, GPP synthase, FPP synthase, and GGPP synthase. GPP synthase condenses one molecule of DMAPP and one molecule of IPP. FPP synthase condenses one molecule of DMAPP with two molecules of IPP in succession. GGPP synthase condenses one molecule of DMAPP with three molecules of IPP in succession. During these repeated condensations, the intermediate prenyl diphosphates are normally bound and not released by the enzymes. The PaIDS1 protein is believed to act like a GGPP synthase, but it releases a significant portion of the GPP formed as an intermediate. The remainder of the GPP is converted directly to GGPP without release of FPP. OPP indicates a diphosphate group.

Diterpenes are derived from a common isoprene precursor, geranylgeranyl diphosphate, via the formation and chemical modification of carbon skeletons. Structural and functional diversity is achieved by the various functions of diterpene cyclases and chemical modification enzymes.

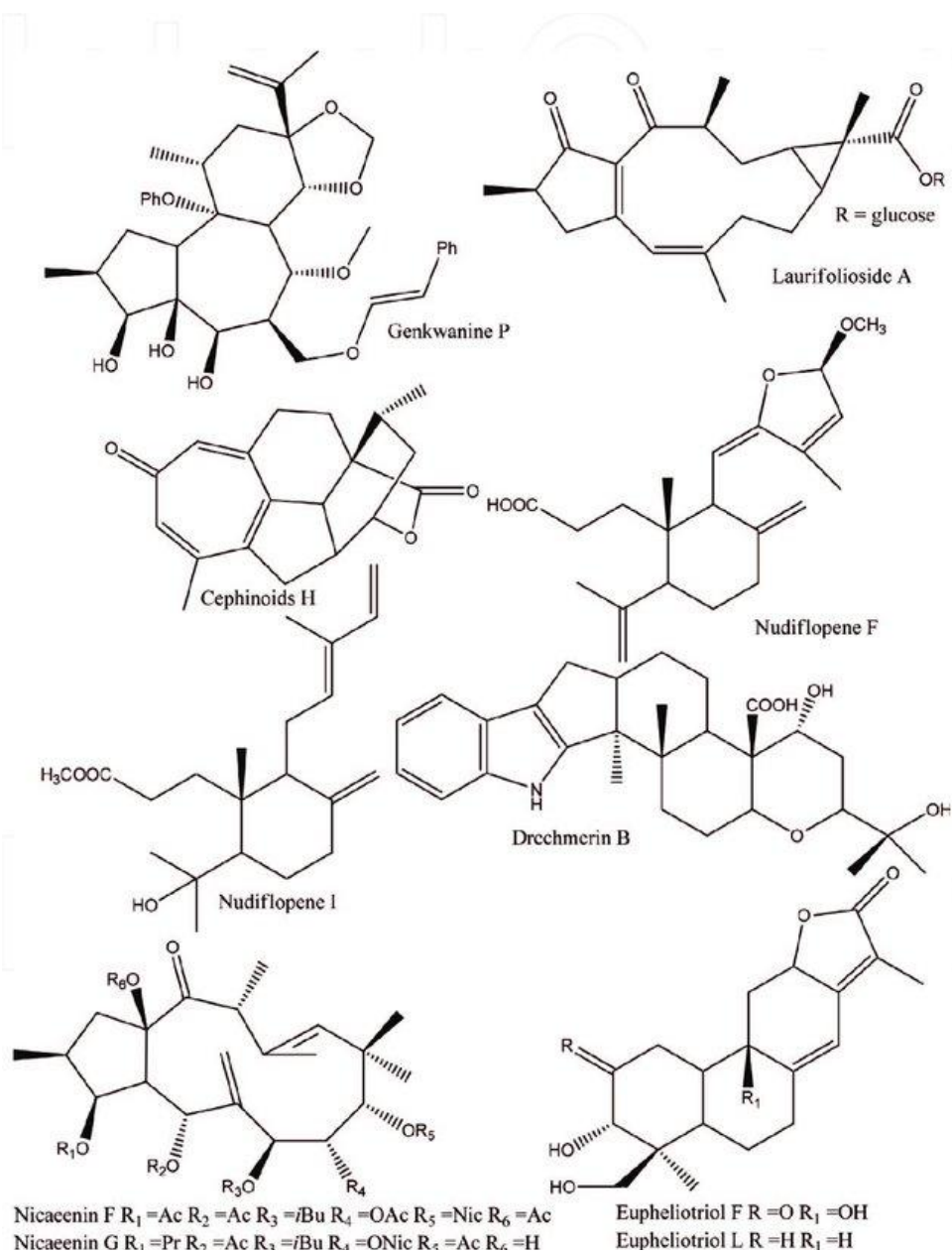


Figure 10. Structure of diterpenes [20].

To date, the cDNAs for a variety of diterpene cyclases responsible for the formation of carbon skeletons or cyclic diphosphate intermediates, such as copalyl diphosphate, have been cloned from higher plants, bryophytes, fungi, and bacteria [21]. Diterpenes have attracted growing attention because of their interesting biological and pharmacological activities. Although thousands of diterpene compounds have been described in nature from terrestrial and marine organisms, only few of them became clinically effective. Overall, the anticancer drug taxol, used in therapy against ovarian, breast, and lung cancer, with its synthetic water-soluble analogue taxotere, is an example of unusual structure discovered from nature and used as medicine.

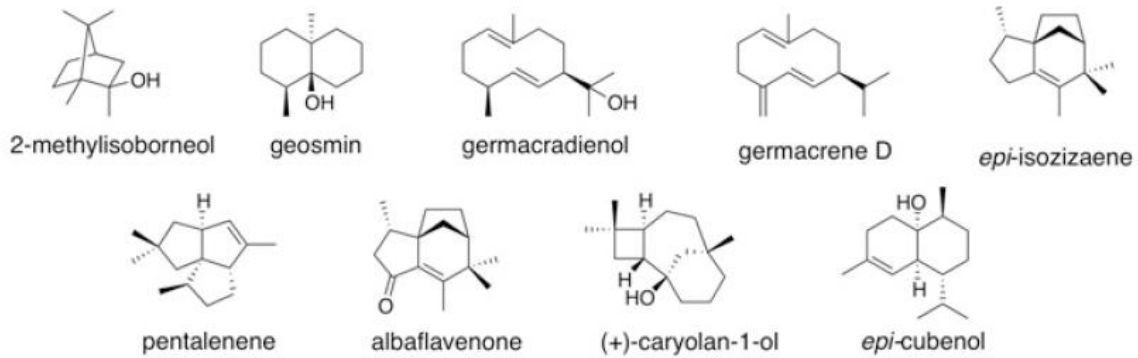


Figure 11. Structure of Major known Terpenes produced by bacteria

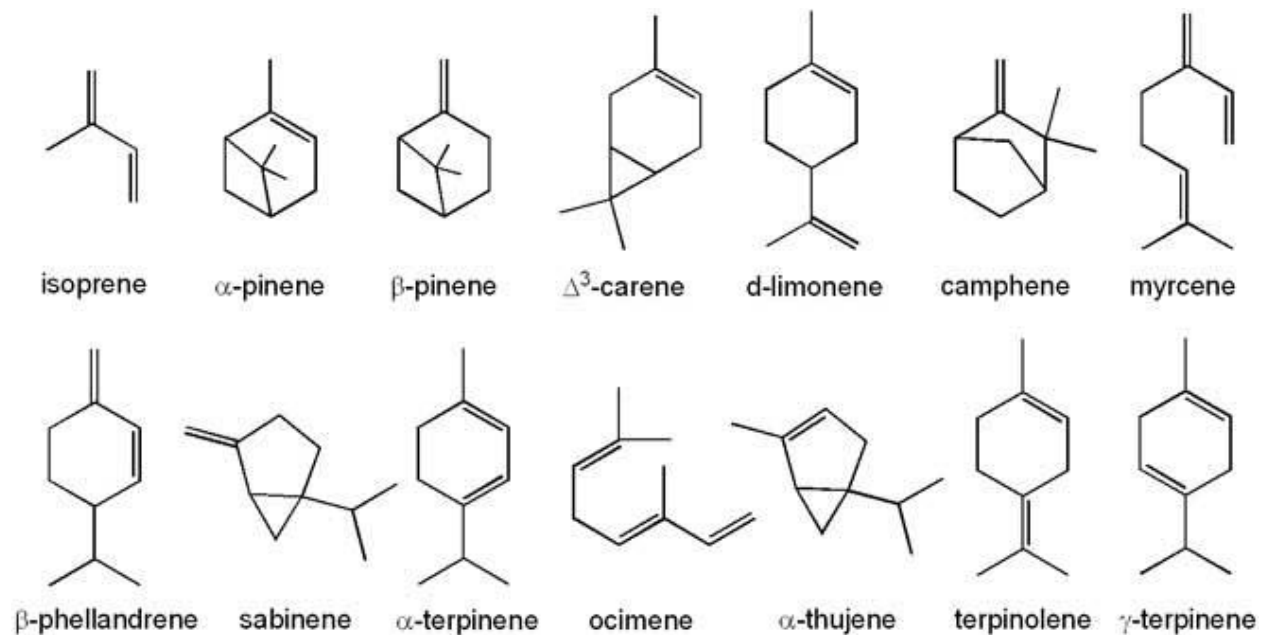


Figure 12. Examples of different terpenes – this diagram shows their chemical structure

Promising diterpenes are the ginkgolides showing potent and selective antagonistic activity toward platelet-activating factor increasing in conditions of shock, burns, ulceration, and inflammation skin diseases. Also used in therapy is the diterpene resiniferatoxin, an ultrapotent vanilloid, isolated from the *Euphorbia resinifera* latex, in clinical trials for bladder hyperreflexia and diabetic neuropathy. The diterpenes used in therapy will be described together with other promising bioactive diterpenes with particular attention to those isolated from plants [22]. Sesterterpenes are terpene molecules containing a C₂₅ skeleton, which are rare among terpene compounds. Many of them are reported from marine fungi, especially those from mangroves, which include neomangicols A–C and mangicols A–G from the Bahamas mangrove fungus *Fusarium* sp. In filamentous fungi, genes coding for the enzymes that catalyze secondary metabolites (SM) synthesis, together with those coding for specific regulatory functions and resistance proteins, are usually contiguously aligned in the genome. C₂₅ sesterterpene synthases were discovered only in recent years. Ophiobolin F synthase (AcOS) was found by accident during genome mining for diterpene synthase from *Aspergillus clavatus* [26].

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