

The function of terpene natural products in the natural world

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As the largest class of natural products, terpenes have a variety of roles in mediating antagonistic and beneficial interactions among organisms. They defend many species of plants, animals and microorganisms against predators, pathogens and competitors, and they are involved in conveying messages to conspecifics and mutualists regarding the presence of food, mates and enemies. Despite the diversity of terpenes known, it is striking how phylogenetically distant organisms have come to use similar structures for common purposes. New natural roles undoubtedly remain to be discovered for this large class of compounds, given that such a small percentage of terpenes has been investigated so far.

The word 'biodiversity' is on nearly everyone's lips these days, but 'chemodiversity' is just as much a characteristic of life on Earth as biodiversity. Living organisms produce thousands and thousands of different structures of low-molecular-weight organic compounds. Many of these have no apparent function in the basic processes of growth and development, and have been historically referred to as natural products or secondary metabolites. The importance of natural products in medicine, agriculture and industry has led to numerous studies on the synthesis, biosynthesis and biological activities of these substances. Yet we still know comparatively little about their actual roles in nature.

Such knowledge is especially lacking for terpenes (also known as terpenoids or isoprenoids), the largest group of natural products. Of the approximately 25,000 terpene structures reported¹, very few have been investigated from a functional perspective. In part this is a legacy of the once widely held belief that all natural products are metabolic wastes. For much of the last century, terpenes were depicted in textbooks as products of detoxification or overflow metabolism. However, starting in the 1970s, a number of terpenes were demonstrated to be toxins, repellents or attractants to other organisms, which led to the belief that they have ecological roles in antagonistic or mutualistic interactions among organisms². Though testing terpenes in natural settings has been difficult, modern genetic and molecular methods are now providing more experimental tools for studying their functions. Here we compile some of the major roles known for terpenes in nature, emphasizing those compounds classically considered to be natural products. Certain specialized groups of terpenes with well-characterized physiological functions—for example, sterols (membrane components, hormones) and carotenoids (photosynthetic pigments and antioxidants)—are not further discussed.

Armaments against antagonists

Perhaps the best way to appreciate the general role of terpenes in the defense of many types of organisms is to consider a large group of terpenes, such as the drimane sesquiterpenes (**Fig. 1**), which are widespread in plants, fungi and certain marine organisms³. Drimanes have potent antibacterial⁴ and antifungal⁵ activity, and they are toxic to insects⁶, nematodes⁷, mollusks and fish⁸. In addition, they deter feeding by insects on plants⁹ and by fish on sponges¹⁰. The mode of action of many drimanes is believed to result from the reaction of the ene-dialdehyde function with biological nucleophiles, which is initiated by attack on the olefin carbon that is β to the aldehyde functionality³. Although the target molecule is not yet clear, drimane feeding deterrence may be a result of direct action on taste receptors. In lepidopteran larvae, these substances block the stimulatory effects of glucose, sucrose and inositol on chemosensory receptor cells located on the mouthparts, and they could also act on receptors in other ways. The hot pungent taste that drimane dialdehydes produce in humans may be a manifestation of the same type of activity.

Besides drimanes, so many other terpene natural products have been reported to act as toxins, growth inhibitors, or deterrents to microorganisms and animals that protection against enemies may indeed be their primary role in nature. For example, various monoterpenes (C_{10}) are toxic to insects¹¹, fungi¹² and bacteria¹³ and serve as feeding deterrents to mollusks¹⁴, insects¹⁵ and mammals¹⁶. However, demonstrating that these compounds have a genuine defensive function in nature is not trivial. Tests must be performed with appropriate doses of terpenes applied to ecologically relevant target organisms in a realistic manner as part of a well-controlled experiment. These conditions are not often met by investigators whose primary goal is to demonstrate activity for pharmaceutical or crop-protection applications. Nevertheless, evidence for the defensive roles of terpenes is increasing with the development of the new discipline of chemical ecology. In the next few paragraphs, we survey some recent examples chosen from different groups of organisms.

Plants. Much work on terpene defensive properties has centered on plant terpenes. In one investigation, larvae of the lepidopteran

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Published online 18 June 2007; doi:10.1038/nchembio.2007.5

Trichoplusia ni were allowed to feed on plants containing latex. Of the plant species tested, *T. ni* was most poisoned by feeding on the milkweed *Asclepias curassavica*, which contains cardenolides (Fig. 1) in its latex canals¹⁷. These steroidal glycosides are toxic to many animals through their inhibition of Na⁺/K⁺-ATPases, but they are used medically in carefully regulated doses to slow and strengthen the heartbeat. After a bout of feeding on this milkweed, larvae of *T. ni* suffer severe spasms and become immobilized, requiring up to three days to recover before they can feed again. The same effects were seen after ingestion of pure cardenolides, but not after feeding on other latex-containing plants lacking cardenolides.

Tests of terpene function can be facilitated by the use of genetically transformed organisms in which terpene levels have been manipulated without an effect on other traits. A recent example involving plants is a study of *Arabidopsis thaliana* engineered to overexpress a terpene synthase¹⁸. These plants emit large amounts of the monoterpene alcohol linalool (Fig. 1), which is normally produced only in trace levels¹⁹. Compared with wild-type *A. thaliana*, the transgenic plants significantly repelled *Myzus persicae* aphids in a choice test, which suggests that emitted monoterpenes could function in plant defense.

Another experimental approach to studying plant terpene function involves the use of elicitors or endogenous signal molecules to modulate terpene accumulation. When methyl jasmonate, a well-known inducer of plant defense responses, was applied to Norway spruce trees, there was an increase in monoterpenes and diterpenes in the trunk resin. Treated trees were colonized less by the bark beetle *Ips typographus* than untreated controls²⁰.

Plant terpenes are also important in resistance to diseases caused by fungi and bacteria. Triterpenoid saponins (Fig. 1) are terpene glycosides with detergent properties that are toxic to fungi because of their ability to complex with sterols in fungal membranes, which leads to the loss of membrane integrity²¹. Mutants of an oat species (*Avena strigosa*) that are deficient in producing saponins are severely compromised in resistance to fungal pathogens compared with wild-type lines²².

Insects. Terpenes also function as protective substances in the animal kingdom, especially for insects. Here the assignment of a defensive role is often less ambiguous than for plants or microbes because the terpenes are usually sprayed directly at enemies. A list of insect terpene defense secretions includes the iridoid monoterpenes of leaf beetles (Fig. 1)²³ and the sticky monoterpene-, sesquiterpene- and diterpene-containing mixture secreted by termites²⁴. A more controversial issue for insect terpene defenses has been to ascertain their biosynthetic origin. Many are chemically very similar to plant products and are obtained from the diet unchanged or in a slightly modified form, such as the iridoid glycosides and cardenolides stored by certain lepidopteran insects²⁵ and the monoterpenes and diterpenes stored by pine sawflies²⁶. Others, such as the iridoids of leaf beetles, are made by the insect, as shown by incorporation of labeled precursors²³ and isolation of genes encoding biosynthetic enzymes²⁷.

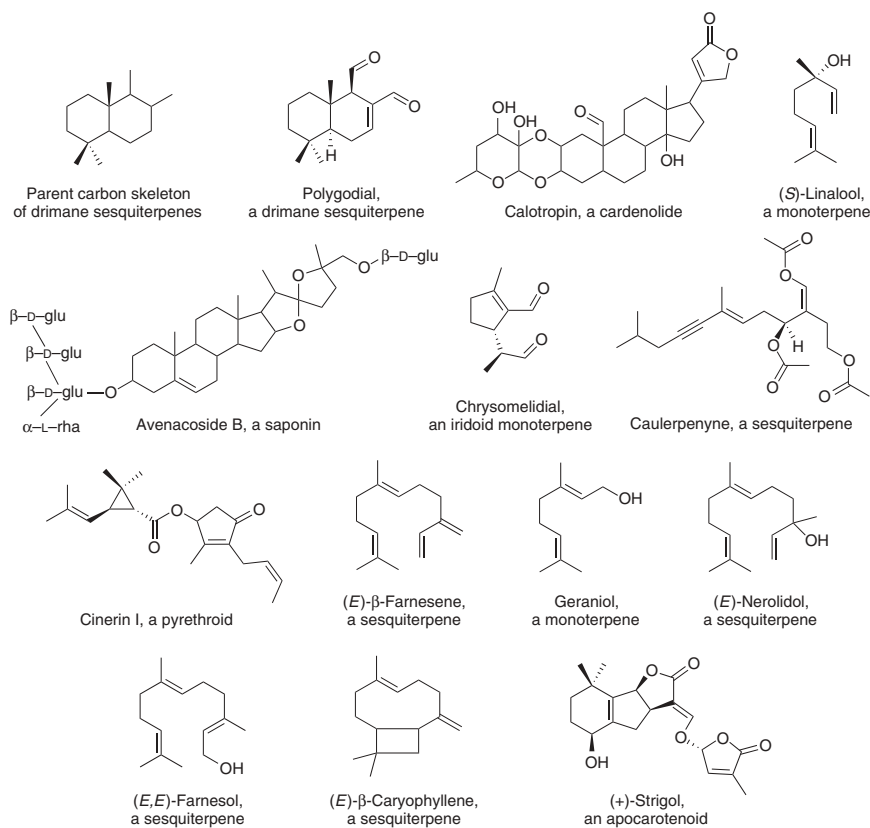


Figure 1 Examples of terpenes with established functions in nature. rha, rhamnose; glu, glucose.

Marine organisms. Terpenes may also act as defenses for a variety of organisms in the marine world, including algae, sponges, corals, mollusks and fish²⁸. A recent example showed that caulerpenyne (Fig. 1), an acetylenic sesquiterpene constituent of green algae, deters feeding by a sea urchin species both in choice tests with living algae and when incorporated into an artificial diet made from freeze-dried algae embedded in agar²⁹. Caulerpenyne and certain diterpenes of marine algae represent unusual dynamic defenses that are stored in the form of polyacetates and rapidly converted into highly reactive 1,4-dialdehydes by esterase action when algal tissue is wounded^{30,31}.

In water, as on land, chemical defenses are typical of organisms that are sedentary, slow-moving or otherwise poorly defended. For example, the opisthobranch mollusks (sea slugs), which lack shells, accumulate a large variety of diterpenes for defense—some acquired from the diet and some biosynthesized *de novo*³². Sedentary marine organisms need defenses not only to combat predators and pathogens, but also to prevent their surfaces from being colonized by bacteria, fungi, diatoms, barnacles, tunicates and bryozoans. Numerous terpenes have been implicated in this phenomenon, including the halogenated ones typical of red algae³³.

Chemical specificity. When confronted with classes of metabolites as large as the terpenes, it is tempting to make broad generalizations about their activity. However, this can be dangerous not only at the level of the whole class, but also when considering similar structures within a class. An instructive example concerns gossypol (Fig. 2), a sesquiterpene dimer found in cotton that is formed from two cadinane units. Wild and domesticated cottons contain gossypol and related terpenoids in glands on their foliage, flower parts, bolls

and roots^{34,35}. Gossypol occurs as a mixture of two enantiomers because of restricted rotation around the central binaphthyl bond. The ratio of (+)- to (-)-gossypol varies widely among cotton cultivars, and each enantiomer has different biological activities. For nonruminant animals, such as rodents, chickens and humans, (-)-gossypol is significantly more toxic than the (+) enantiomer³⁶. In fact, most biological activities of gossypol seem to be a consequence of this enantiomer. (-)-Gossypol inhibits the growth of cancer cells more than the (+) enantiomer³⁷, is a more effective antiamebic agent³⁸, and inhibits male fertility in humans³⁹. Although the precise molecular mechanism of gossypol action is not known, it has been recently found that (-)-gossypol binds to the antiapoptotic protein Bcl-X_L in the outer mitochondrial membrane, thereby inducing mitochondrial-mediated apoptosis in various systems^{40,41}. By acting directly on the mitochondria, (-)-gossypol provides the ability to overcome Bcl-X_L-mediated apoptosis resistance.

In contrast to (-)-gossypol, the (+) enantiomer shows little if any toxicity to nonruminant animals. But cotton plants containing high levels of (+)-gossypol are also resistant to insect damage. Diet feeding studies on the generalist lepidopteran herbivore *Helicoverpa zea* showed that (+)-gossypol is as inhibitory as racemic or (-)-gossypol⁴². Similarly, the two enantiomers are equally effective in inhibiting the growth of the cotton fungal pathogen *Rhizoctonia solani*⁴³. The inhibitory effects of (+)- and (-)-gossypol on insects and fungi may result from a mode of action common to the two enantiomers, such as protein binding mediated by Schiff base-type linkages between the aldehyde residue of gossypol and the amino groups of proteins.

The differences between the activity of (+)- and (-)-gossypol are not just of academic importance. The toxicity of (-)-gossypol makes cottonseeds, which are excellent sources of oil and protein, unsafe for consumption by humans and monogastric animals. Plant breeders have long been attempting to remove gossypol from cottonseed without decreasing its levels in parts of the plant usually attacked by insects or pathogens. A recent demonstration of the tissue-specific RNA interference silencing of a gossypol biosynthetic gene encoding (+)- δ -cadinene synthase was quite successful in this regard⁴⁴. Breeders may also wish to maximize the level of (-)-gossypol in seeds for its use as a male contraceptive in humans.

Mode of action. A full understanding of the function of terpenes in defense requires knowledge of how these substances work at the molecular level. In previous sections, we have already mentioned what is known about the mode of action of drimanes, cardenolides and saponins. Another familiar terpene class is the pyrethroids (Fig. 1), a group of cyclopropyl monoterpene esters from *Chrysanthemum* plants. Both naturally occurring pyrethroids and synthetic analogs are important commercial insecticides because of their limited persistence in the environment and negligible toxicity to mammals and birds. Pyrethroids disrupt the insect nervous system by acting on

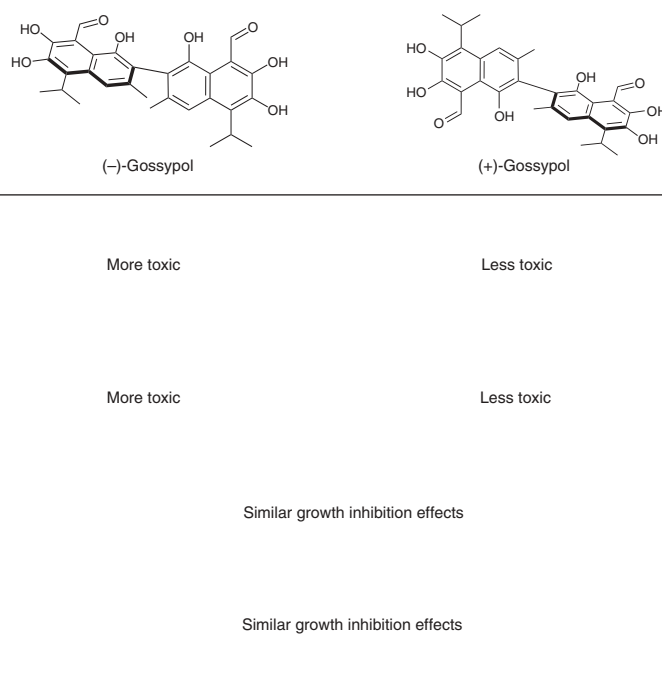


Figure 2 Structurally similar terpenes often have very different ranges of biological activities. This is exemplified by the dimeric sesquiterpene gossypol, whose two atropoisomers (due to restricted rotation around the central binaphthyl bond) differ significantly in their effects on herbivores, pathogens and isolated cells.

the voltage-sensitive sodium channel protein of the nerve membrane⁴⁵. By inducing repetitive discharge in nerves in place of single impulses, the nervous system becomes hyperexcited, which results in rapid, uncoordinated movement and paralysis.

Considering the large number of terpene defenses present in nature, we know very little about their mode of action at the molecular level. The highly lipophilic nature of many of these compounds suggests that their principal targets are cell membranes and their toxicity is caused by loss of chemiosmotic control^{46,47}. A related possibility is that terpenes synergize the effects of other toxins by acting as solvents to facilitate their passage through membranes. The monoterpenes from the plant *Porophyllum gracile* were shown to increase the toxicity of a polyacetylene plant defense compound to the lepidopteran *Ostrinia nubilalis*⁴⁸. The same effect was seen against microorganisms: a mixture of monoterpenes and sesquiterpenes from the traditional Chinese herb *Perilla frutescens* enhanced the toxicity of the drimane sesquiterpene polygodial against a range of bacteria and fungi⁴⁹. This phenomenon is now being exploited by pharmacologists seeking new ways to achieve drug delivery through the skin⁵⁰.

Even when the mode of action of toxic terpenes is known at the molecular level, this does not necessarily imply that we understand how they act in a defensive role (or if they even have a role in defense at all). For example, the sesquiterpene lactone artemisinin from *Artemisia annua* has become one of the most widely used antimalarial drugs in the world. This endoperoxide kills all asexual stages of the malarial parasite, *Plasmodium falciparum*, by inhibiting the Ca²⁺-ATPase of the sarco-endoplasmic reticulum (Fig. 3)^{51,52}, but there is no information on whether it protects *A. annua* against herbivores and pathogens. Similarly, the blockbuster anticancer diterpene paclitaxel (Taxol), isolated from yew, kills tumor cells by binding to tubulin, which interferes with microtubule dynamics and arrests

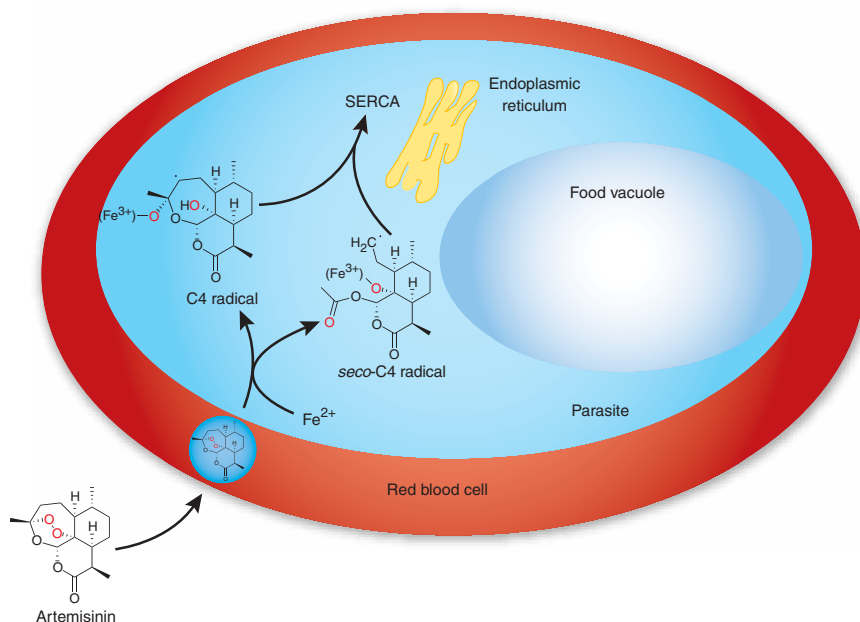


Figure 3 Mode of action of the *Artemisia annua* sesquiterpene lactone artemisinin against the malarial parasite. Artemisinin is transported from the red blood cells of the host into the parasite (*Plasmodium falciparum*) via parasite-derived membrane vesicles. Once inside the parasite, it interacts with ferrous iron (Fe^{2+}), leading to cleavage of the peroxide bridge (shown in red) and formation of transient radical intermediates. The radicals specifically and irreversibly bind and inhibit the sarco-endoplasmic reticulum Ca^{2+} -ATPase (SERCA) of the parasite, thereby inhibiting its growth. The natural role of artemisinin in *A. annua* is still unknown. Figure modified with permission from ref. 98.

mitosis⁵³. Though the taxane diterpenes of the yew are very likely to be plant defenses (given that these are the principal natural products of a genus of plants known to be very toxic to grazing animals), nothing is known about their protective function.

Messages for mutualists

Not every organism encountered is an enemy; many are partners involved in mutually beneficial interactions. Here too terpenes may have critical roles in interactions among organisms by serving as a medium of communication among species. Most monoterpenes and sesquiterpenes are good conveyors of information over distances because they are low-molecular-weight, lipophilic molecules with high vapor pressures at ordinary temperatures. In addition, the vast structural variety of terpenes present allows messages to be very specific.

Most of our examples of terpene-mediated communication are in plant-insect interactions⁵⁴, but terpenes also have important functions within species as pheromones. Among insect species, they serve as sex, aggregation, trail and alarm pheromones^{55,56}. For example, the sesquiterpene (*E*)- β -farnesene (**Fig. 1**) acts as an alarm pheromone in aphids. Released during predator attack, this acyclic hydrocarbon causes aphids to stop feeding, disperse, and give birth to winged (rather than wingless) forms, which leave their host plants^{57,58}. By releasing their own (*E*)- β -farnesene, plants could exploit these effects to repel aphids and attract aphid enemies, although this has not yet been clearly documented under natural conditions^{59,60}.

Plants are immobile for most of their life cycle and often rely on other organisms to disperse pollen and seeds. For this purpose, volatile compounds released from flowers and fruits seem to serve as advertisements to attract pollinators and dispersal agents. Terpenes

are one of the major components of fruit and flower volatiles⁶¹, but proof that a specific terpene attracts a specific animal under natural conditions has not often been obtained⁶². Perhaps the best evidence of the role of terpenes in attracting pollinators comes from studies of insect olfaction. Gas chromatography in combination with electroantennogram detection has shown that terpenes are indeed perceived by pollinating insects⁶³. Detailed investigation of the olfactory system of *Manduca sexta* (the tobacco hornworm) revealed that this pollinator has a group of receptor cells that respond strongly to certain oxygenated monoterpenes and sesquiterpenes, such as geraniol, (*E*)-nerolidol and farnesol⁶⁴ (**Fig. 1**). The olfactory receptor cells transfer the information to the antennal lobe, the primary olfactory center of the brain, which consists of spherical structures called glomeruli. Sensory input from terpenes was found to be processed in a lateral cluster of glomeruli of *M. sexta*⁶⁵, and specific glomerular clusters responding to terpenes were also reported in other flower-visiting moths^{66,67}.

Flowers and fruits are not the only plant organs involved in volatile communication with other organisms. Researchers have discovered that herbivore feeding on foliage induces the emission of blends of volatiles in which terpenes are major components^{68,69}.

These blends serve as an odoriferous call for help, attracting predators and parasitoids that attack herbivores^{68–70}. Recent field and laboratory experiments have helped identify specific monoterpenes and sesquiterpenes that are involved in mediating this attraction^{70–72}.

It is not just feeding by herbivores that attracts their enemies to plants. Amazingly, the mere act of laying an egg can have the same effect. For example, when the pine sawfly (*Diprion pini*) lays its eggs on pine twigs, the volatiles released attract a wasp that parasitizes the sawfly eggs⁷³. The sesquiterpene (*E*)- β -farnesene (**Fig. 1**) seems to be the principal attractive component of this blend⁷⁴, but it is only active against a background of other pine terpenoids⁷⁵.

Volatile terpenoid communication is not restricted to the above-ground parts of plants. Recently it was reported that insect attack on maize roots triggers the release of a sesquiterpene, (*E*)- β -caryophyllene (**Fig. 1**), which attracts nematodes that prey on insect larvae⁷⁶. This sesquiterpene hydrocarbon can apparently diffuse through the soil matrix at a rate that is fast enough to serve as a useful signal. Nonvolatile terpenes involved in below-ground communication include strigol and other strigolactones, which are of apocarotenoid origin⁷⁷. These compounds are released by plants to stimulate the growth of arbuscular mycorrhizal fungi, which leads to symbiotic associations that can greatly improve plant prospects for nutrient acquisition⁷⁸.

Terpene messages from plants may also have other, unintended recipients. Enemies, such as herbivorous insects or parasitic plants, may use terpenes to locate their hosts. For example, larvae of the lepidopteran *Spodoptera frugiperda* use volatile terpenes released upon wounding to help find their food plants⁷⁹. Seedlings of the parasitic plant dodder (*Cuscuta pentagona*) grow toward nearby tomato plants guided by a blend of monoterpenes⁸⁰, whereas other parasitic plants (*Striga* spp. and *Orobancha* spp.) use strigolactones, the cues for

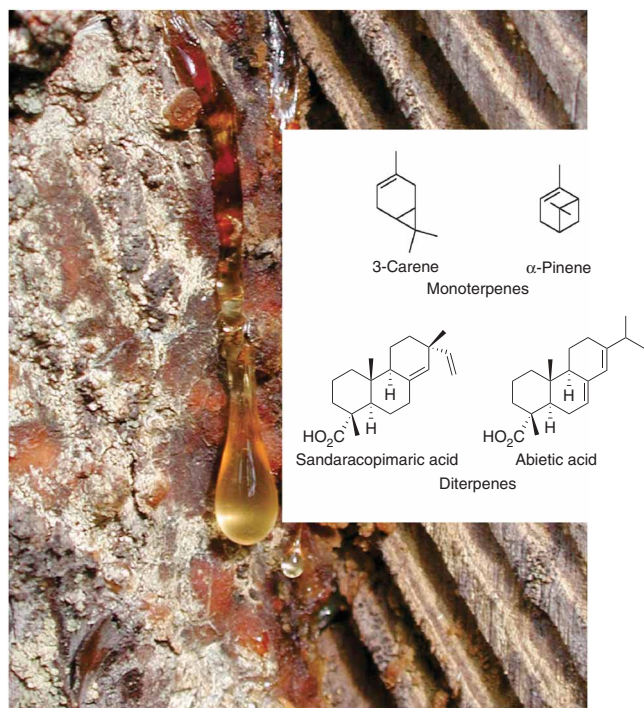


Figure 4 Mixtures of terpenes, such as conifer resin, may act synergistically in defense. The resin of conifers contains two principal classes of terpenes: monoterpene olefins and diterpene acids. When the resin ducts are severed by an attacking herbivore or pathogen, the more volatile monoterpenes are thought to act as solvents enabling a rapid flow of the less volatile diterpene acids out of the resin ducts⁹³. The diterpene acids are toxins and feeding deterrents to herbivores, and they also polymerize on exposure to oxygen, thereby sealing the wound. The resin monoterpenes also act as herbivore toxins and fungal growth inhibitors, but are quite volatile at ordinary atmospheric pressure and temperature. However, their evaporation from the wound site is thought to be reduced by the presence of the less volatile diterpene acids⁹⁴. Photograph of Scots pine resin by M. Riederer, Würzburg, Germany.

promoting mycorrhizal associations in the soil mentioned above, as germination stimulants⁸¹. Plant terpene emission may also be an internal cue for the plant to indicate the presence of an herbivore and allow induction of defenses in neighboring tissues. A terpene-rich blend of volatiles from herbivore-damaged lima bean leaves stimulates nearby leaves to increase their secretion of a nectar that attracts herbivore enemies⁸². Finally, terpene volatiles can even alert other plants in the vicinity to the presence of herbivores. Although airborne communication among neighboring plants has been a controversial topic for many years, there are now multiple examples in the literature in which plants were found to respond to aerial cues put out by herbivore-attacked neighbors by increasing their own defenses or priming the machinery involved in defense production^{83–85}.

The function of mixtures

No discussion of the role of terpenes in nature would be complete without some attention to the enormous diversity of structures observed both within and among individual organisms. Here we consider why organisms usually produce complex mixtures of terpene natural products instead of just one or two compounds. At the molecular level, the prevalence of terpene mixtures may be a consequence of the properties of the biosynthetic pathway that produces them (see Commentary in this issue by Fischbach and Clardy; p. 353). However, at the organismal level, the production of mixtures may be thought of as a direct way to enhance terpene function. If terpenes are used in communication, for example, the release of mixtures may result in messages with more specificity and a higher information content.

For terpenes used in defense, a number of proposals have been put forth regarding the possible value of mixtures. For example, for organisms with a wide range of enemies, a diverse combination of terpene defenses may help achieve simultaneous protection against numerous predators, parasites and competitors. Mixtures have also been suggested to impede the ability of enemies to evolve resistance⁸⁶. This possibility has not yet been critically examined for terpenes, but

research on *Bt* toxins in transgenic broccoli has shown that the development of resistance in a lepidopteran herbivore is slower on plants having two different *Bt* toxins compared with plants with a single *Bt* toxin⁸⁷. The presence of complex mixtures also increases the probability that individual organisms in a population will have a unique composition of defenses. Possession of a novel terpene composition may have defensive value against enemies already adapted to circumvent some of the terpene defenses prevalent in a given population⁸⁸.

Another much discussed advantage of defense mixtures is that the individual components can act synergistically to provide greater toxicity or deterrence than the equivalent amount of a single substance. For instance, the antifungal activity of two individual steroidal glycoalkaloids from potato was enhanced several-fold by the addition of as little as 10% of the second steroidal glycoalkaloid⁸⁹. Such synergism may be attributed to the ability of some defenses to increase the persistence of others by inhibiting detoxification or excretion processes in adapted enemies^{90,91}. Alternatively, mixtures of defenses may be deterrent to enemies for longer periods than single compounds as a result of effects at the sensory level⁹². Mixtures of terpenes containing compounds with different physical properties may allow more rapid deployment or longer persistence of defenses. An example of such synergism seems to occur in conifer resin (Fig. 4), which is a mixture of (i) monoterpene olefins (C_{10}) with antiherbivore and antipathogen activity, and (ii) diterpene acids (C_{20}) that are toxic and deterrent to herbivores. The lower molecular weight monoterpenes are believed to act as solvents enabling the rapid transport of the higher molecular weight diterpene acids from resin ducts to the site of enemy attack⁹³. The resin monoterpenes themselves are readily volatilized on exposure to the atmosphere. However, their evaporation from the site of attack may be retarded by the presence of the less volatile diterpenes⁹⁴.

Instead of synergy, the components of mixtures may show “contingency,” a term coined for the antibiotic secondary metabolites of *Streptomyces* spp. to indicate compounds that are not classical synergists but that do have similar biological activity and are independently deployed by producing organisms⁹⁵. A group of sesquiterpenes isolated from the plant *Landolphia dulcis* may be considered contingent because molecular modeling of these substances suggested that they all interact with the same macromolecular target, but in slightly different ways; they also have a range of physicochemical properties allowing access to the target through various types of biological barriers⁹⁶. These attributes are exactly what might be expected for a mixture of defense compounds designed to act on a single target. Another view of mixtures is that the individual components do not necessarily all have to have biological activity at a given stage of evolution, but they are produced nevertheless to increase the chances of being able to respond to future challenges⁹⁷. Testing the validity of these proposals will

require extensive investigations, but the rewards are likely to be high given that mixtures are such a prominent feature of terpene natural products. Thus understanding the rationale for mixture production should make a major contribution to understanding the natural roles of terpenes.

Conclusions

All living organisms manufacture terpenes for certain essential physiological functions and therefore have the potential to produce terpene natural products. Given the many ways in which the basic C₅ units can be combined together and the different selection pressures under which organisms have evolved, it is not surprising to observe the enormous number and diversity of structures elaborated. However, the biological roles of the vast majority of terpenes are still unknown. Functional investigations have lagged far behind those directed at chemical synthesis, biosynthesis or practical applications in medicine, agriculture and industry. The idea that terpene natural products have important biological functions has taken hold only recently, and there are considerable difficulties in testing these compounds in natural settings. Fortunately, the powerful toolboxes of modern molecular biology and chemical biology now enable experimenters to use organisms whose terpene production has been carefully manipulated by genetic knockout, transformation, or use of low-molecular-weight elicitors. Recent advances in analytical chemistry also help in functional studies by providing a much more comprehensive view of the spectrum of terpenes present in and around individual organisms than was previously available. With these resources at hand, practitioners of the emerging discipline of chemical ecology are well equipped to learn more about the roles of terpenes in the natural world in the near future.

ACKNOWLEDGMENTS

The authors are grateful to K. Falk for help with references and figures, and to the Max Planck Society (J.G.), the German National Science Foundation (J.G.), the European Commission (J.G.), and the US National Science Foundation (N.D.) for supporting their research on terpenes.

COMPETING INTERESTS STATEMENT

The authors declare no competing financial interests.

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