# Learning Organic Chemistry Through Natural Products

## 4. Structure and Biological Functions

*N R Krishnaswamy*

**Some interesting examples of the linkage between the structure and biological function of secondary metabolites in plants and animals are described.**

The primary activities of a natural product chemist involve the isolation of a naturally occurring compound, determination of its structure and stereochemistry and finally its synthesis in the laboratory to confirm the structure. But this is not the end of the story. In a sense it is only the beginning since the *chemistry* of a natural product holds the key to answer the most important question: "Why do these compounds occur in nature?". It is logical to presume that a naturally occurring compound has some biological function to perform and there should be a connection between its chemistry and biological properties. Indeed, it was believed even at the very beginning of organic chemistry that certain classes of compounds of natural origin such as amino acids and proteins, lipids, carbohydrates and the nucleic acids - constitute the molecular basis of life. Their structures are tailor-made for their specific biological roles and no living

N R Krishnaswamy was initiated into the world of natural products by T R Seshadri at University of Delhi and has carried on the glorious tradition of his mentor. He has taught at Bangalore University, Calicut University and Sri Sathya Sai Institute of Higher Learning. Generations of students would vouch for the fact that he has the uncanny ability to present the chemistry of natural products logically and with feeling.

Biologists classify naturally occurring organic compounds into three types: (1) primary metabolites, (2) semantides and (3) secondary metabolites. The biological functions of the first two types are fairly well-known and they hold the key to fundamental biochemical reactions which control life processes. Secondary metabolites include the terpenoids, the alkaloids, the flavo-noids and related compounds which occur very widely in higher plants. According to Rembold ( J Eder, H Rembold, *Naturwiss.*, 1992, *79*, 60) signal transmissions in nature through chemicals is only a part of the larger phenomenon of biosemiotics.

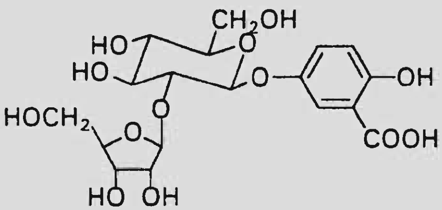
The plant *Mimosa asperta* has been mentioned in an ancient manuscript 'Plant Geography' written by Theophrastus during the reign of Alexander the Great. That the leaves of *Tamarindus indica* take nocturnal 'rest' was also known to the ancients. This observation was first recorded by Andro-sthenes in 325 BC. In 1729, the astronomer de Mairan observed that in *Mimosa pudica* the pinnules close and open at the usual time. The term 'Circadian Rhythm' to describe such pheno-mena was suggested by Hallberg.

The ogre Kumbhakarna of Ramayana fame was Ravana's younger bro-ther. He was cursed by Brahma as a result of which he had to remain asleep for a long period at a time. He had to be woken up out of a deep slumber to fight against Rama and his army, and was killed by Rama on the battle field.

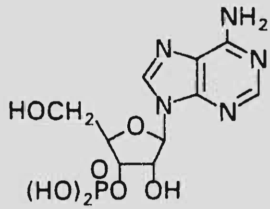
organism can exist without these compounds. However, for a long time the biological functions of some other classes of compounds such as alkaloids, terpenoids, polyphenolics were not clearly known and there was widespread belief that these compounds, classified as *secondary metabolites,* were waste products of metabolism! A lot of recent evidence shows that several of these secondary metabolites not only have important functions to perform but are also responsible for imparting unique and characteristic biological traits to the organisms in which they occur.

## The Turgor Effect

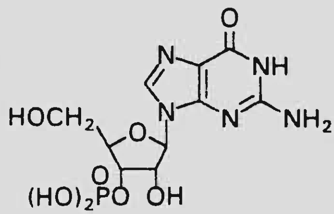
Certain plants such as the 'Touch-me-not' *(Mimosa pudica)* the Tamarind *(Tamarindus indica), Acacia karroo* and *Mimosa asperata* are 'alert' and sensitive to external stimuli and subtle changes in incident light. They owe this capacity, termed the *Turgor effect*, to the presence of a few secondary metabolites classified as the turgorins. These compounds are presumably produced from readily available precursors *only* when the plant's external 'antennae' sense a possible danger or a change in daylight. The precursors themselves are ineffective in producing the turgor effect. After the lapse of a reasonable period of time the plant 'wakes up' after the turgorins are metabolised to inactive compounds. In this case one can see a phenomenon based on what one may call common sense! A specific compound with a particular biological effect is produced only when there is a need for it. If a turgorin had been present in the plant as a stable and permanent chemical constituent, the Touch-me-not plant would have become a botanical Kumbhakarna and a boon would have become a curse! The turgorins are phenolic and purine glycosides and the turgor effect is a direct consequence of their structures. Being glycosides they have a strong affinity for water. Their production or accumulation at a particular site, therefore, brings about the 'flow' of water and its structuring as in ice



*Aryl - Glycoside*



*3′ - AMP*



*3′ - GMP*

formation (a result of hydrogen bonding). The consequent change in water pressure produces an osmotic effect resulting, for example, in a shrinking of the pinnate leaf cells. The visible result is that the leaves close; they open up again when the turgorins are metabolised to inactive compounds. One of these leaf-movement factors isolated from *Mimosa pudica* has been characterised as the 5-riboglucoside of 2, 5-dihydroxy-benzoic acid. In this plant, leaf movement is also brought about by two nucleotides which have been identified as adenosine 3′-monophosphate (3′-AMP) and guanosine 3′-monophosphate (3′-GMP). Monoglucosides of gallic acid with one or two sulfate groups on the sugar ring have been recognised as the major leaf-movement factors of *Acacia karoo*.

## Semiochemicals

It is now becoming increasingly clear that secondary metabolites are partly responsible for some of the species-specific characteristics of plants and insects. For instance, the ability of a species to interact in a specific manner with other forms of life in any given environment can often be traced to a specific secondary metabolite that is characteristic of the species. Thus, these compounds regulate plant-plant, plant-insect, plant-vertebrate, insect-insect interactions, etc., in an eco-system. Collectively, such

The ability of a species to interact in a specific manner with other forms of life in any given environment can often be traced to a specific secondary metabolite that is characteristic of the species.

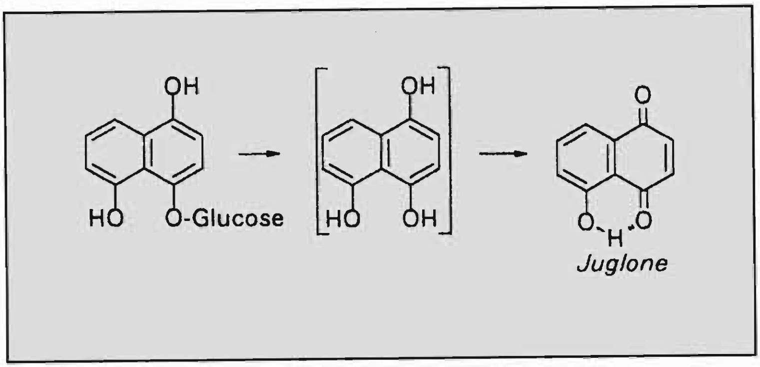
*Parthenium hysteroporus*, more commonly known as Congress grass (because of its white coloured heads) is believed to have been brought to India along with a consign- ment of wheat under the PL-480 scheme. Since then it has spread to almost all parts of the country and has become a plant menace. Another 'colonizer' but less aggressive is *Eupatorium odoratus* which is mostly confined to the state of Kerala where it is popularly known as Communist green! This plant also belongs to the family of Asteraceae.

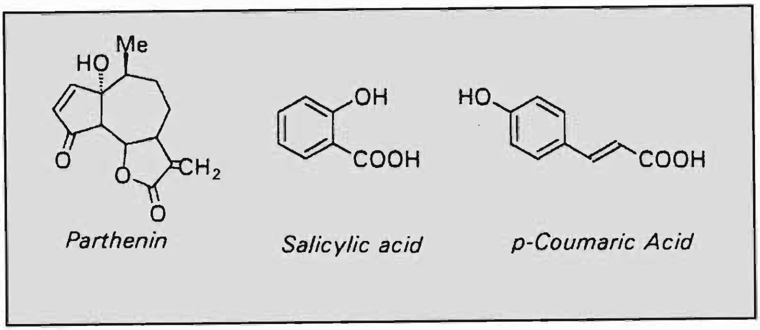
*Parthenium hysteroporus* owes its aggressiveness mainly to the presence of sesquiterpene lactones such as parthenin and certain cinnamic acid derivatives which are plant-growth inhibitors.

compounds are known as *semiochemicals* as they are the chemical mediators in a complex network of signal-communication in any eco-system. These include different types of insect pheromones and allelochemicals. A few interesting examples are described in the following paragraphs.

## Allelochemicals

The system of communication network through chemicals between members of a plant community is known as *allelopathy*. It is a common observation that most plants within a heterogeneous commune individually maintain healthy growth. However, there are certain plants which effectively inhibit the growth of *other* species in their neighbourhood. One such notorious colonizer is *Parthenium hysteroporus* which belongs to the family Asteraceae (Compositae). The plant owes its aggressiveness mainly to the presence of sesquiterpene lactones such as parthenin and certain cinnamic acid derivatives which are plant-growth inhibitors. Another plant which is capable of protecting its territorial rights is the Walnut tree, botanically known as *Juglans nigra* . The leaf canopy of this tree provides a cover under which most other plants do not grow. But this plant is not as aggressive as Parthenium and is eco-friendly to certain plants such as the Kentucky blue-grass (*Poa pratensis*), which normally grow under a Walnut tree. The allelopathic effect of the Walnut is due to the presence of the 4-*O*-glucoside of 1, 4, 5-trihydroxynaphthalene in the leaves. Being a water-soluble compound, it gets washed off the foliage by rain water and dew drops. When it comes into contact with the microorganisms in the soil under the tree, it undergoes cleavage and oxidation to yield 5-hydroxynaphthoquinone, known as *Juglone*, which is a specific phytotoxin. In this example one can see the 'intelligent' use of simple chemical principles in the production of a toxic compound by a plant

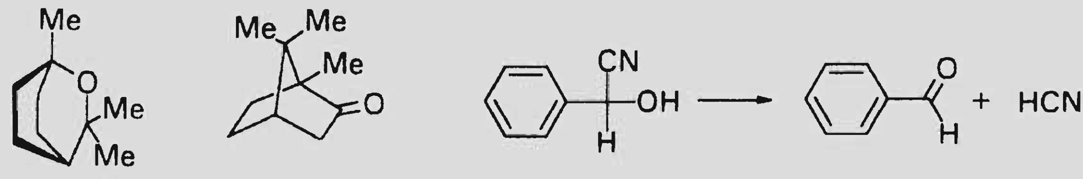



outside its own 'body'. The precursor of the toxin has a sugar 'cap' which can be easily removed and a 1, 4-dihydroxy benzene moiety which has a low oxidation potential. The precursor itself is non-toxic and does not interfere with the normal growth of the tree.

The Oak tree, *Quercus falcata* also produces a simple water soluble allelopathic agent, salicylic acid. Other phenolic acids, such as *p*-hydroxycinnamic acid, also possess plant-growth inhibitory activity and are secreted along with some quinones by plants such as *Adenostema fasciculatum* and *Arctostaphylos glandulosa*. These two plant species are shrubs which are natives of the California chapparal where they inhibit the growth of other herbaceous plants. However, once in about twenty years the aerial parts of these shrubs get burnt in the California fire cycle, enabling the dormant seeds of other

The Oak tree, *Quercus falcata* also produces a simple water soluble allelopathic agent, salicylic acid.




*1,8-Cineole* *Camphor* *Mandelonitrile* *Benzaldehyde*

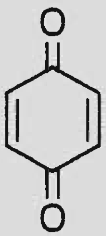
herbaceous species to germinate. Thus, soon after the break-out of the fire, these herbs flourish, grow to maturity and shed seeds which get embedded in the soil. By this time, the aggressive *Adenostema* and *Arctostaphylos* shrubs would have regained their territories and their autocratic rule, supported by *p*-coumaric acid and the quinones, would continue for another twenty years!

In contrast to the Walnut and Oak trees, the leaves of *Salvia leucophylla* produce a volatile oil comprising of cineole, camphor and related compounds. The oil which forms an azeotrope[1] with water gets volatilised, like the oil of *Eucalyptus*, into the atmosphere and then gets absorbed by the dry soil. The low concentrations of these compounds in the soil are enough to inhibit the germination and growth of grass and herbs which would have otherwise formed a thick undergrowth soon after the onset of the winter rains.

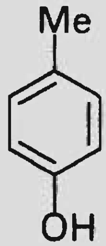
[1]Azeotrope is a mixture of liquids in which the boiling point remains constant during distillation, at a given pressure, without change in composition.

## Defensive Secretions of Insects

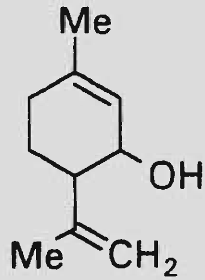
There are several ways in which insects protect themselves against possible predators and adverse climatic conditions in their natural habitats. One mode of defence is to project a 'scary' physical appearance, such as donning a red coat which serves as a warning signal to predators because of the association of the colour with proven vicious anthropods such as the centipede. For example, the slow moving, quite harmless millipedes sport this colour so as to confuse a



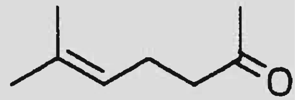
p-Benzoquinone



p-Cresol



Isopipertinol

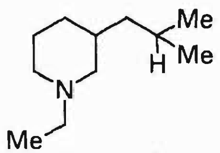


6-Methyl-5-hepten-2-one

predator which could mistake the millipede for a centipede at first glance. But this deception may not always work and the millipede does need a second line of defence. And what can be more lethal than a chemical in a warfare! Millipedes are found in large numbers in moist situations, particularly in the sub-soil under deciduous trees. They are larger than the centipedes and much more sluggish in their movement and hence more susceptible to attack by insectivores. There are different orders, genera and species among the millipedes and the chemicals used by them for defence are equally varied. Millipedes of the order *Polydesmus,* when attacked by a predator or otherwise disturbed, secrete mandelonitrile which breaks up into benzaldehyde and hydrogen cyanide. Millipedes of the order *Julia* use *p*-benzoquinone for their defence against predators. This lachrymatory compound also possesses anti-microbial activity. Another millipede produces *p*-cresol for its defense.

Insects require chemicals not only for defending themselves against predators but also to protect themselves from possible ‘accidents’ such as from drowning. An illustrative example is the innovative use of a surface-active chemical by the water-beetle, *Stenus coma*. This tiny blue-green insect which is only 5 mm long and weighing a grand 2.5 mg is capable of swimming on water at the incredible speed of 50 to 75 cm per

Insects require chemicals not only for defending themselves against predators but also to protect themselves from possible ‘accidents’ such as from drowning



*Stenusin*

second! It needs protection during its search for food along river banks since it may otherwise fall into the flowing water. What enables this tiny creature to perform such an amazing feat is its abdominal secretion which resembles, in smell, the oil of Eucalyptus. This oil obtained from 1000 beetles has been found to contain 0.8 mg of a mixture of 1, 8-cineole, isopipertinol, 6-methyl-5-heptenone and a tertiary amine, stenusin. Stenusin is only sparingly soluble in water but has a high spreading pressure because of its high surface activity. It gives the beetle the protection it needs when its underparts are exposed to the microflora in the water. The oil spreads on water and enables the beetle to glide on its surface. Thus, this little beetle knows enough chemistry to keep it floating and protect itself from water borne microorganisms!

In addition to the compounds mentioned in the text, certain types of millipedes use more complex compounds such as dialkyl quinazolinones and nitro pyrrolizidine for their defence. These compounds resemble some alkaloids of plant origin.

## Suggested Reading


H Schildnicht. Chemical Ecology - A Chapter Of Modern Natural Products Chemistry, *Angew. Chem. Int. Ed. Engl.*, 15 : 214. 1976.

T Swain. Secondary Compounds as Protective Agents. *Ann. Rev. Plant Physiol.*, 28: 479. 1977.

J B Harborne. Introduction to Ecological Biochemistry. Academic Press. New York. 1982.

E L Rice. Allelopathy, 2nd ed., Academic Press. New York. 1982.

M Luckner. Secondary Metabolism in Microorganisms, Plants and Animals, 2nd ed., Springer-Berlag. Berlin. 1984.

L F Alves Chemical Ecology and the Social Behavior of Animals. Progress in the Chemistry of Organic Natural Products, W Herz, H Grisebach, G W Kirby, Ch Tamm. (Eds), Vol 5, pp 1-85, Springer-Verlag, Berlin. 1988.

G D Prestwitch, Chemical Defence and Self-Defence in Termites, Natural Product Chemistry. Atta-ur-Rahman. (Ed), pp 318-329, Springer- Verlag, Berlin. 1988.

D H Williams, M J Stone, P R Hanck, S K Rahman. Why are Secondary Metabolites Biosynthesized? *J Nat Prod.*. 52: 1189. 1989.

P J de Vries. Singing Caterpillars, Ants and Symbiosis. *Scientific American*, 56 : 267 . 1992.



**Address for correspondence**
N R Krishnaswamy
No.12, 9th Main Road,
Banashankari 2nd Stage,
Bangalore - 560 070,
India.