

Chapter 1

Natural Products—An Introduction

Natural products are organic and inorganic compounds that are found in various types of natural sources—plants, microbes and animals. These natural products can be organism itself (plant, animal, and microorganism), any part of an organism (leaf or flower of plant; an isolated gland or other organ of animals) and extract or pure compound (alkaloids, coumarins, steroids, etc). However, in practice, the term natural product refers to secondary metabolites, small molecules (molecular weight <1500 amu), produced by an organism, but not strictly necessary for the survival of the organism.

It has been estimated that well over 3,00,000 secondary metabolites exist in nature. These mediate certain functions that help in their survival and reproductive ability. Alkaloids, such as morphine; eicosanoids, such as prostaglandin E₁ and antibiotics, such as erythromycin and penicillins, are good examples of secondary metabolites.

Classification of Natural Products

There is no rigid scheme for classifying natural products—their immense diversity in structure, function, and biosynthesis are too great to allow them to fit neatly into a few simple categories. Initially, the natural products are classified into two broad divisions: (i) Primary metabolites (occur in all organisms) and (ii) Secondary metabolites (occur only in certain organisms). The primary metabolites are organic molecules that have an intrinsic function; essential for the survival of the organism that produces them. Examples of primary metabolites include the core building block molecules (nucleic acids, amino acids, carbohydrates, lipids, etc. In contrast, secondary metabolites are not essential for growth but do increase the competitiveness of the organism within its environment. These are usually produced in response to stress include steroids, terpenes, alkaloids, etc. In practice, however, workers in the natural products field often speak of five main classes of natural products: terpenoids and steroids, fatty acid-derived substances and polyketides, alkaloids, nonribosomal polypeptides, and enzyme cofactors (Fig 1.1).

- **Terpenoids and steroids:** This includes a vast group of substances—more than 35,000 are known—derived biosynthetically from isopentenyl diphosphate. Terpenoids have an immense variety of apparently unrelated structures, while steroids are modified terpenoids, having a common tetracyclic carbon skeleton. These are biosynthesized from the triterpene, lanosterol.

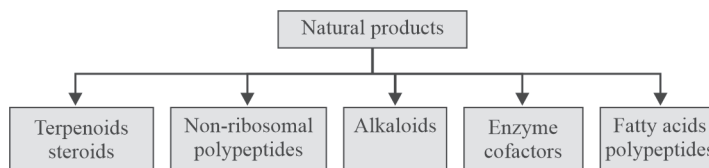


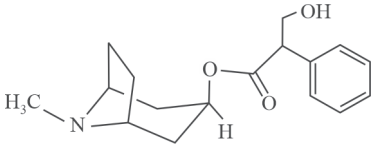
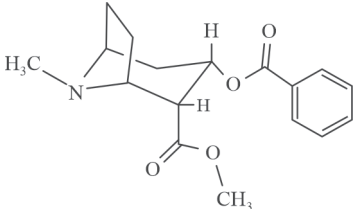
Fig. 1.1: Classification of natural products

- **Alkaloids:** Like terpenoids, there are a large diverse class of compounds, with more than 12,000 examples known at present. Alkaloids are organic substances that contain nitrogen atom, typically in a ring structure and are derived biosynthetically from amino acids.
- **Fatty acid-derived substances and polypeptides:** About more than 10,000 of these are known, which are biosynthesized from simple acyl precursors such as acetyl CoA, propionyl CoA, and methylmalonyl CoA. Natural products derived from fatty acids, such as eicosanoid prostaglandin E₁, generally have most of the oxygen atoms removed, but polyketides, such as the antibiotic erythromycin A, often have many oxygen substituents.
- **Non-ribosomal polypeptides** are peptide like compounds that are biosynthesized from amino acids by a multifunctional enzyme complex without direct RNA transcription. Non-ribosomal peptide antibiotics (e.g. bacitracin), cytostatics (e.g. bleomycin), and immunosuppressants (e.g. ciclosporin) are in commercial use.
- **Enzyme cofactors** do not fit one of the other general categories of natural products and are usually classed separately.

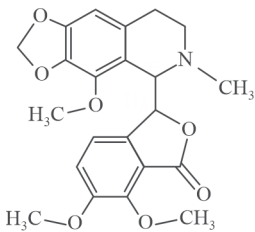
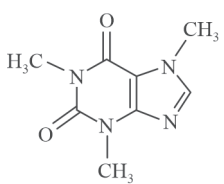
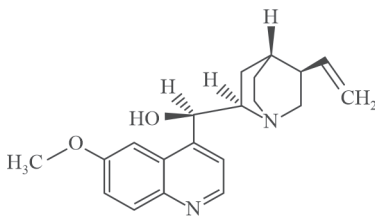
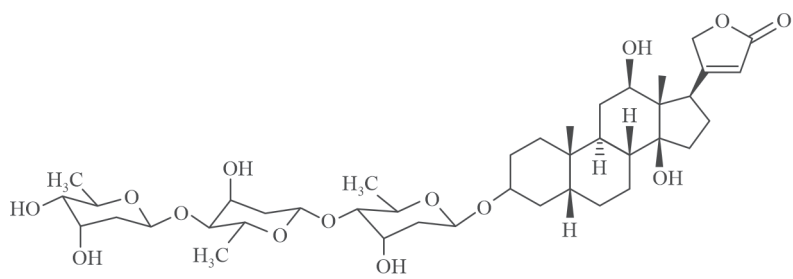
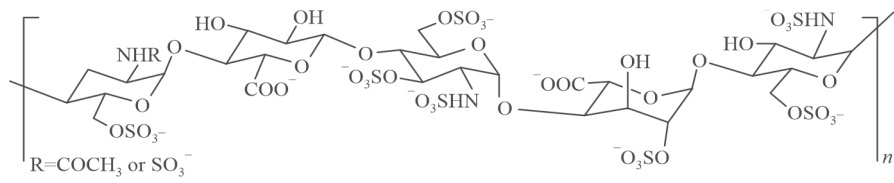
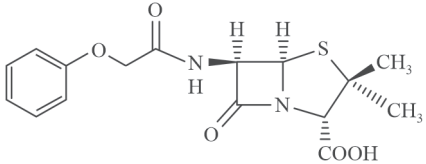
Natural Products in Medicine

Natural products have been a potential source of therapeutic agents for thousands of years. An impressive number of modern drugs have been derived from natural sources. Over the last century, a number of top selling drugs have been developed from natural products. For example, anticancer drug—vincristine from *Vinca rosea* and Taxol from *Taxus brevifolia*, narcotic analgesic—morphine from *Papaver somniferum*, antimalarial drug—artemisinin from *Artemisia annua*, and antibiotic penicillins from *Penicillium* sp. are just a few examples (Table 1.1)

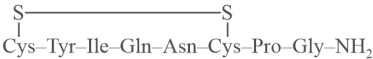
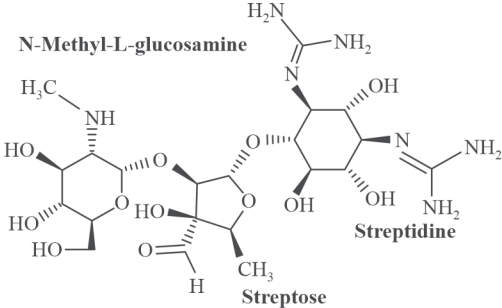
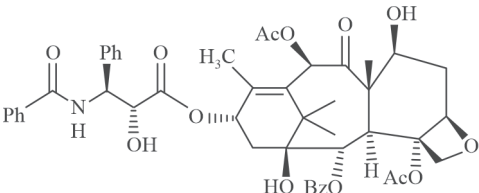
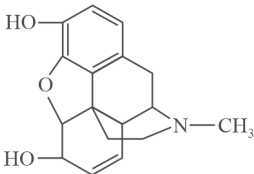
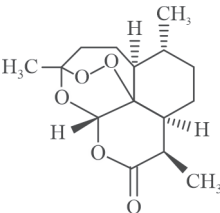
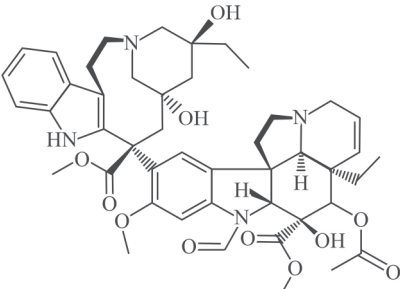
Table 1.1: Uses of natural products as medicine

Name	Chemical Structure	Origin (use)
Atropine (alkaloid)		<i>Atropa belladonna</i> (ophthalmic applications, antispasmodic)
Cocaine (alkaloid)		<i>Erythroxylon coca</i> (local anaesthetic, stimulant)

(Contd.)

Name	Chemical Structure	Origin (use)
Noscapine (alkaloid)		<i>Papaver somniferum</i> (cough remedy)
Caffeine		Tea, coffee (stimulant)
Quinine (alkaloid)		<i>Cinchona ledgeriana</i> (antimalarial)
Digoxin (steroidal glycoside)		<i>Digitalis purpurea</i> (heart medicine)
Heparin (carbohydrate) (mucopolysaccharide)		Liver/lung tissue of cattle (anticoagulant)
Phenoxymethylpenicillin (peptide)		<i>Penicillium</i> sps. (semisynthetic antibiotic)

(Contd.)

Name	Chemical Structure	Origin (use)
Oxytocin (peptide)	 <chem>Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Gly-NH2</chem>	Brain (hormone)
Streptomycin (carbohydrate)		<i>Streptomyces griseus</i> (antibiotic)
Taxol (Paclitaxel)		<i>Taxus brevifolia</i> (anticancer)
Morphine		<i>Papaver somniferum</i> (analgesic)
Artemisinin		<i>Artemisia annua</i> (antimalarial)
Vincristine		<i>Catharanthus roseus</i> (anticancer)

Apart from natural-product-derived modern medicine, these products are also used directly in the herbal pharmaceutical industry. The use of these natural products is growing rapidly throughout the world.

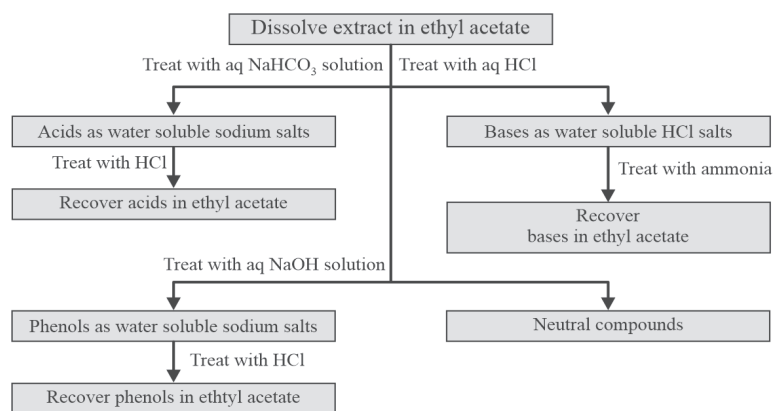
Isolation of Natural Products

Secondary metabolites, with some exceptions, occur very less in amounts, about 0.01% of the dry weight of the plant. Usually extraction of 1 kg of dry plant material is likely to yield less than 100 mg of a natural product. These compounds may be unstable and present as part of a complex mixture. The isolation, separation and purification of these natural products require considerable skill. The source of a secondary metabolite requires proper identification and so a voucher specimen needs to be retained. Within the same species there are sometimes chemotypes, each with a particular composition. Some compounds are found in the roots, some are components of the bark, and others may be found in the leaves, the flowers or the fruits. Some compounds play a seasonal role in the plant, for example as insect antifeedants. Thus, the part of the plant and the place and date on which the plant was collected should all be recorded.

Microorganisms are usually deposited in national culture collections. The production of microbial metabolites often depends upon the medium on which the microorganism is grown and on other fermentation details.

Some fungal metabolites are retained in the fungal mycelium, whilst others are excreted into the broth. Insects, marine organisms and fungi that were collected in the wild may have stored and modified compounds which they had obtained from their food. Natural products may be obtained from the crushed biological material by **extraction** with a solvent such as petroleum ether, chloroform, ethyl acetate or methanol. Several solvents of increasing polarity may be used. Thus, lipid material (waxes, fatty acids, sterols, carotenoids and simple terpenoids) can be extracted with non-polar solvents such as petroleum ether, but more polar substances such as the alkaloids and glycosides are extracted with methanol, aqueous methanol or even hot water. Many alkaloids are present as their salts with naturally occurring acids such as tartaric acid.

Commercial extractions may use tonne quantities of plant material, and a range of different extraction procedures including steam distillation. Most of the isolation procedures still employ basic extraction techniques like infusion, decoction, maceration, percolation, soxhlet, and reflux extraction. Recently, commercial procedures have been developed using supercritical carbon dioxide as a mild solvent, but because of the pressures involved, this requires quite complicated apparatus. The initial extraction is then followed by a **separation** into acidic, basic and neutral fractions. A typical separation procedure is given in Scheme 1.1. A solution of the extract in an organic solvent (such as



Scheme 1.1: Separation of an extract into acidic phenolic, basic and neutral fractions

ethyl acetate) is shaken with an inorganic base (such as aqueous sodium hydrogen carbonate) to remove the carboxylic acids as their water-soluble sodium salts. The more weakly acidic phenols may only be extracted with a sodium hydroxide solution. Extraction of the original solution with an acid such as dilute hydrochloric acid removes the bases such as the alkaloids as their salts. The neutral compounds remain behind in the organic phase. The acid and the phenols may be recovered from the aqueous solution of their sodium salts by treatment with dilute hydrochloric acid and re-extraction with an organic solvent, and the bases may be recovered by treatment of their salts with ammonia and re-extraction.

Although some abundant natural products may be obtained merely by extraction, a simple fractionation or partition and crystallization, the majority are obtained after further careful chromatography. A typical example might involve chromatography on silica or alumina and elution with increasing concentration of ethyl acetate in petroleum ether. The chromatographic separation may be monitored by a bioassay or by thin layer chromatography (TLC). A number of useful spray reagents have been developed, which produce colored TLC spots, indicative of particular classes of compounds.

During the isolation of natural products, various types of reaction such as ester hydrolysis, autoxidation, rearrangement, etc. may occur, leading to the formation of artefacts. Hence, efforts are made to keep the mild condition.

SHORT AND LONG QUESTIONS

1. Classify the natural products? Illustrate the general techniques to isolate the phytoconstituents of various categories.
2. Comment on the role of natural products in the discovery of drugs. Mention the examples of naturally occurring substances used as medicine.

MULTIPLE CHOICE QUESTIONS

1. **Synthesis of most of the complex natural products is a challenging task. Which of the following factors is not a contributing factor to this?**
 - a. Presence of variety of functional groups present
 - b. Presence of multicyclic or unusual ring systems
 - c. Lack of asymmetric centres
 - d. Variety of substituents
2. **Which of the following is known as Ginseng of India?**
 - a. *Penax ginseng*
 - b. *Withania somnifera*
 - c. Tulsi
 - d. Giloe

Answers

1. (c) 2(a)