As shown in Figure 7.1, the powerful antibiotics penicillin and vancomycin are representatives of nonribosomally synthesized peptide natural products that have great utility in modern medicine.

Terpenoids comprise a highly diverse class of secondary metabolites, whose members are constituted by combinations of five-carbon units. These segments are commonly referred to as "isoprenoid units" that are biogenetically derived from one of two alternative pathways, either through mevalonic acid or deoxyxylulose phosphate. Traditionally, these compounds have been characterized as monoterpenes (C10), e.g., menthol and camphor; sesquiterpenes (C15), e.g., artemisinin; diterpenes (C20), e.g., paclitaxel (Taxol); and so on to sesterterpenes (C25), and triterpenes (C30). The obvious structural diversity is derived from cation-induced rearrangements of the nascent isoprenyl chain to form a large variety of cyclic frameworks.

Polyketides are the result of an exceptionally versatile biosynthetic pathway that assembles polyfunctional compounds by sequential condensation of small carboxylic acid units, followed by a variety of other steps, such as reductive processing, "tailoring" reactions, and cyclization. The range of structural diversity of polyketides is so vast that it is difficult to summarize with only a few examples, so for illustration two of the best known antibiotic polyketides, tetracycline and erythromycin, are shown in Figure 7.1.

These biosynthetic origins remain basically the same across the phylogenetic spectrum; however, the distribution of various pathways is highly dependent on the type of organism. Polyketides and nonribosomally synthesized peptides, particularly those with antimicrobial activity have primarily been isolated from bacteria and fungi. Higher plants are historically the most prolific sources of terpenes and alkaloids. Since higher plants are readily accessible they were the first sources to be explored for medicinal properties.

7.2 HISTORICAL PERSPECTIVE

Plants have been used as medicines for centuries, according to folklore, often without any perceptible efficacy. Plant materials were processed for medicinal use by chopping and grinding into powders or through aqueous extraction to make teas, smoking, or chewing. Often mixtures of plant products were combined ostensibly to create the most beneficial medicines. While the majority of these products were not effective, it was accepted practice, and other than faith healing there was no real alternative.

Despite the difficulties encountered by administering mixtures of plant products in these crude preparations, several have yielded medicinally useful products upon purification. Opium, a dried concentrate of the milky latex derived from the poppy, *P. somniferum*, has been used for thousands of years as an analgesic. Recreational smoking of opium for its euphoric effect became popular in Europe in the early nineteenth century. Morphine (see Figure 7.1), which is the major active alkaloid in opium, is a powerful pain medicine, but owing to its addictive properties is mainly prescribed for the management of pain in terminal illnesses.

Malaria is an infectious disease caused by protozoan parasites of the genus *Plasmodium*. Symptoms of malaria have been treated with a number of plant preparations. Cinchona bark was originally discovered to have antimalarial properties in South America in the early 1600s and was soon imported to Europe where it was widely prescribed. Chemical investigations in the early 1800s by Pelletier and others led to the isolation of purified alkaloids possessing the antimalarial properties of the plant materials. Quinine (Figure 7.1), the major active principle obtained in this work, soon became the preferred treatment for symptoms of malaria and was manufactured through large-scale isolation from the bark. The advent of substituting purified chemicals for crude plant preparations marked a turning point for pharmaceutical discovery. Quinine continues to have practical use in the treatment of certain resistant forms of *Plasmodium falciparum*.

In Chinese traditional medicine, *Artemisia annua* or qinghao has been employed as an antimalarial agent for many centuries. In this case, the sesquiterpene lactone artemisinin (Figure 7.1), containing a rare peroxide bridge, was isolated from the plant material and shown to possess effective