recombinant fusion proteins in which a tumor-selective antibody fragment is fused to sTRAIL or sFasL ligands of death receptors, also fail when the targeted tumor cells are resistant to apoptosis due to one or more defects in death receptor or caspase apoptosis pathways. In these cases, to have apoptosis induction with minimal effects on normal cells, the combinatorial use of various pro-apoptotic agents working along different or complementary apoptotic signaling routes is necessary. The strategies to achieve a longer efficacy for anticancer treatments rely on the identification of specific cancer-related aberrancies in each patient, and they require the development of reliable, cost-effective, and high-throughput diagnostic tools. In this respect, laser-capture microscopy and DNA microarray technology permit the obtention of large quantities of gene expression data from individual cancer cells, although it is still difficult to extract meaningful information from these data and to connect them to tumor-specific phenomena or drug information.

7 NATURAL PRODUCTS IN CANCER CHEMOTHERAPY

Since the beginning of chemotherapy, plants, microorganisms, and, more recently, marine organisms of various types have traditionally represented a main source of cytotoxic anticancer agents.[58] Nature is a source of potential chemotherapeutic agents and also of lead compounds that have provided the basis and inspiration for the semisynthesis or total synthesis of effective new drugs. The discovery of several effective anticancer agents from plants may be attributed, directly or indirectly, to a history of use of the relevant plant in traditional medicine. From the mechanistic standpoint, microtubules are a very frequent target of cytotoxic natural products.

A large number of drugs in clinical use as anticancer drugs are of natural product origin, and it has been estimated that approximately 80% of new chemical entities with small-molecule structures introduced during the period from 1950 to 2010 in this field were natural products or were natural-product inspired (small molecules, in turn, represent 77% of the total).[59] Despite this statistic, pharmaceutical companies have neglected the development of potential natural drug candidates. The main reason for this reluctance lies primarily in supply problems, which make necessary the development of synthetic routes often long and difficult to scale up because of the structural complexity of natural products. It is becoming increasingly apparent, however, that the unguided production of vast libraries of compounds is unlikely to result in the identification of new drugs, whereas natural products have in general several functional groups that are located in a precise 3D position, providing specific interactions with target molecules. It is often assumed that secondary metabolites have been optimized through evolution and that, consequently, they may be considered as highly advanced lead compounds in which further optimization of activity is difficult.[60] Nevertheless, in many cases, some parts of the complex structure of a natural product act only as a framework to position determined atoms, and simpler analogs may be developed without considerable loss of activity. For this reason, structural modification of natural products is often directed to find a possible simplest portion that maintains most of the biological activity—that is, its pharmacophoric unit. One example of this approach is the discovery of the antitumor agent eribulin (E-7389) in the development of synthetic strategies to obtain halichondrin B. Studies revealed that deletion of a large portion of this natural product and the replacement of the unstable lactone by a ketone function did not significantly affect its antimitotic properties (see Chapter 9, Section 2.1.2).[61] Eribulin was approved to treat several cancers and is under clinical trials for other types.