Chapter 5
Medicinal Plants as a Source of Alkaloids

Valentina Laghezza Masci, Stefano Bernardini, Lorenzo Modesti, Elisa Ovidi, and Antonio Tiezzi

Abstract Plants are an important source of biomolecules widely used in medical treatments, and among such products, the alkaloids are a very interesting and complex group. The definition of the term "alkaloid" is still a cause of controversy due to the similarity of some of these natural molecules with other secondary compounds. From a biological point of view, alkaloids are a group of chemicals actively involved in different biological processes of plants, animals, and microorganisms at different cellular levels. In medical science alkaloids are nitrogenous compounds, derived from vegetables origin, characterized by high molecular masses and complex structures. A possible classification of alkaloids is based on their biological and ecological activity, chemical structures, and biosynthetic pathway. They are grouped according to the shape and origins, and in this view three main groups of alkaloids can be distinguished: true alkaloids, protoalkaloids, and pseudoalkaloids.

Keywords True alkaloids · Protoalkaloids · Pseudoalkaloids · Pharmaceutical properties

5.1 Introduction

For a long time, plants play an important role in medical treatments, and thanks to their wide biochemical diversity, the use is being extensively studied especially as source of biomolecules. To date, about 40% of modern monomolecular drugs derive directly or indirectly from plants and their secondary metabolites (Bernardini et al. 2017). Some plant molecules are marked as pharmaceutical regulators; however, in most cases, in absence of clinical tests, the empiric experience matured in traditional medicine during hundreds or thousands of years can be considered testimony of their efficacy.

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D. Egamberdieva, A. Tiezzi (eds.), *Medically Important Plant Biomes: Source of Secondary Metabolites*, Microorganisms for Sustainability 15,
https://doi.org/10.1007/978-981-13-9566-6_5

The plant organisms use the products of secondary metabolism as intermediaries with the surrounding environment. Among such products alkaloids are a very interesting and complex group present in different biotopes, and although relatively common in all the kingdoms of living organisms, four fifths of known secondary metabolites come from the plant kingdom (Kim and Buell 2015). Two hundred years of scientific research has not yet fully explained the connections between alkaloids and life, nor has it explained why these diverse chemicals are produced and degraded by organisms or why they have such a very large spectrum of biological activities. This is probably due to the link among plants, soil, and the environment and contributing to develop numerous adaptation mechanisms (Aniszewski 2007).

Alkaloids appeared for the first time in the worldwide scenery in 1805, when a German apothecary assistant named Friedrich Sertürner isolated an impure form of the molecule of morphine, which is still today one of the most important and widely known alkaloid (Bynum and Porter 1994a; Courtwright 2009; Krishnamurti and Rao 2016), thus allowing a very important progress in the fields of chemistry and pharmacology (Sneader 1990; Aniszewski 1994a; Dias et al. 2012; Veeresham 2012). In the following years, the extraction method developed by Sertürner allowed pharmacists to isolate many other alkaloid molecules, such as brucine, strychnine, febrifuge, quinine, caffeine, and veratrine (Fig. 5.1) (Bynum and Porter 1994a; Bynum and Porter 1994b; Dias et al. 2012; Veeresham 2012).

The term "alkaloid" was coined in 1819 by the German apothecary Wilfred Meißner who noticed that such compounds seemed "like alkali" (Clayden et al. 2001).

However, although several attempts since the time of their discovery have been performed, especially within the academic world, the definition of the term "alkaloid" is still a cause of controversy due to the similarity of some of these natural molecules with other secondary compounds. Biologists, for instance, consider alkaloids as pure and perfect natural products: a very general picture of such molecules describe them as compounds biologically active, with a chemical heterocyclic structure containing nitrogen, which can possibly have pharmacological, medicinal, or ecological use (Aniszewski 1994b). The huge biological and chemical differences between such compounds make it difficult to give a general definition of alkaloid groups without adding exceptions, objections and derogations (Koskine 1993). There have been different ways to define the alkaloid molecules: for Winterstein and Tier (1910) the alkaloids were compounds having a chemical structure with a basic composition, heterocyclic nitrogen atoms and amino acid derivative classified according to the order of a greater or less toxicity on the central nervous system and the source plants; Waller and Nowacki (1978) instead focused their attention on the presence of nitrogen connected to at least two carbon atoms and of at least one ring not necessarily heterocyclic and affirmed that the alkaloids could not be structural units of macromolecular cellular substances, vitamins, or hormones; in more recent times, Sengbush (2003) defines alkaloids simply by emphasizing the presence within the molecules of bases that contain nitrogen and that most of them are drugs.

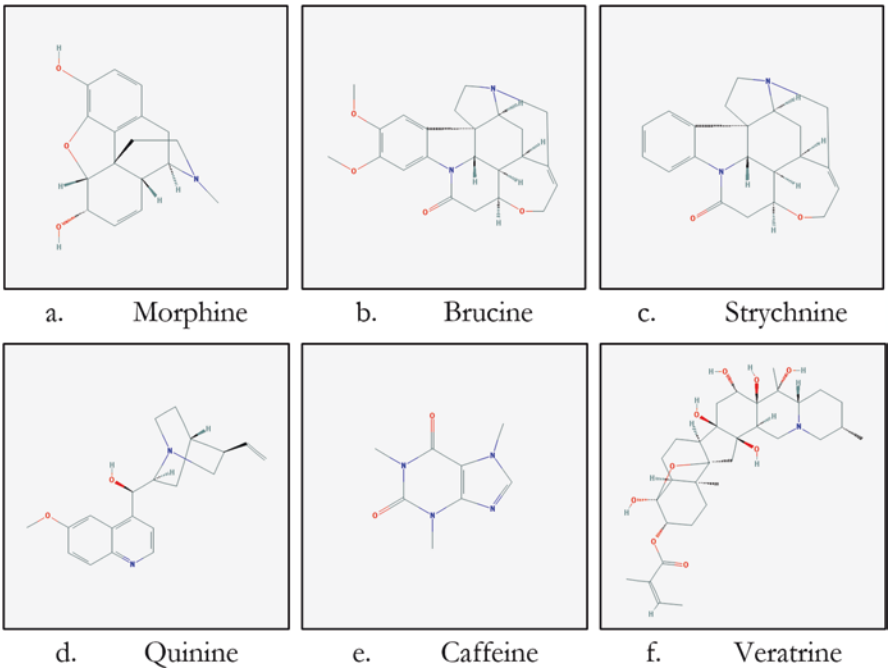

Fig. 5.1 Chemical structures of the earlier discovered alkaloids. (**a**) Morphine, (**b**) brucine, (**c**) strychnine, (**d**) quinine, (**e**) caffeine, (**f**) veratrine

Starting from these assumptions, the alkaloids are defined using the features which better qualify the activity or the structures of such molecules. From a biological point of view, alkaloids are a group of chemicals which are actively involved in different biological processes of plants, animals, and microorganisms at different cellular levels. In medical science substances are considered alkaloids when they are nitrogenous; derived from vegetables, characterized by high molecular masses and complex structures, including heterocycles containing primary, secondary, or tertiary bases or a quaternary ammonium groups (Aniszewski 2007); and soluble in ethanol, benzene, ether and chloroform much better than in water. Moreover, other distinctive features of alkaloids are their power to create intense physiological actions, which allows their application as curative drugs, as well as the possibility to result highly toxic for organisms even when used in very little doses. Different definitions of alkaloids from a medical point of view are also available, and an authoritative definition, among the others, is provided by the National Library of Medicine (NCBI 2005). Another definition of alkaloids has been provided by chemists, who defined such substances as a group of heterocyclic nitrogen compounds which conserve their basic chemical properties and show a strong physiological activity and often result to be toxic, although it has been also asserted that such definition is subject to few exceptions as reported in literature (Jakubke et al. 1994).

Although there are some small differences among them, all such definitions are very similar and sometimes identical.

In any case, whatever the definition, alkaloids are natural compounds synthetized by living organisms as a consequence of their own metabolism and providing biological, chemical, and pharmacological activities which have allowed to develop drugs to fight, and sometimes defeat, many different diseases. Nowadays thousands of natural compounds and derivatives are assessed as alkaloids and new molecules belonging to such group are constantly discovered at the rate of about 100 every year. Alkaloids can be found as acid, salts, amides, and esters and in combination with sugars or also in quaternary salts or tertiary amine oxides (Aniszewski 2007).

5.2 Classification of Alkaloids

A possible classification of alkaloids is based on their biological and ecological activity, chemical structures, and biosynthetic pathway. Considering the biological activity, alkaloids can be divided into different groups: neutral or weakly basic molecules (lactams and certain N-oxides), animal-derived alkaloids (produced by anurans, mammalians, and arthropods), marine alkaloids, moss alkaloids, fungal and bacterial alkaloids, and non-natural alkaloids (structural modified or analogues), the last of which has been continuously growing in recent years as a consequence of bio-organic and stereochemistry research and of the increasing demand for new molecules for possible production and pharmaceutical application.

Anyway, alkaloids classification is generally based on the common molecular precursors, depending on the molecular pathway by which the molecules have been synthetized, and, considering their structures, they are then grouped according to shape and origins. In this view three main groups of alkaloids can be distinguished: true alkaloids, protoalkaloids, and pseudoalkaloids, the only group containing alkaloids not derived from amino acids (Aniszewski 2007).

True alkaloids occur in a limited number of species and families of plants in the free state, as salts and as N-oxides, and are produced as a consequence of the condensation of decarboxylated amino acids with a nonnitrogenous structural moiety. They are highly reactive crystalline substances, generally white solid (with the exception of nicotine that is a brown liquid) able to form water-soluble salts when they are united with acids, bitter in taste, and biologically active even in low doses. Precursors of this kind of molecules are L-ornithine, L-lysine, L-phenylalanine/L-tyrosine, L-tryptophan, and L-histidine (Dewick 2002), and some of the most famous true alkaloids are cocaine, quinine, dopamine, morphine, and usambarensine (Fig. 5.2).

Protoalkaloids are a little group of compounds characterized by very simple chemical structure, consisting in a closed ring, in which the N atom is not included in the heterocyclic (Jakubke et al. 1994). Such kind of alkaloids derived from L-tyrosine and L-tryptophan, and good examples of them are hordenine, mescaline, and yohimbine (Fig. 5.3).

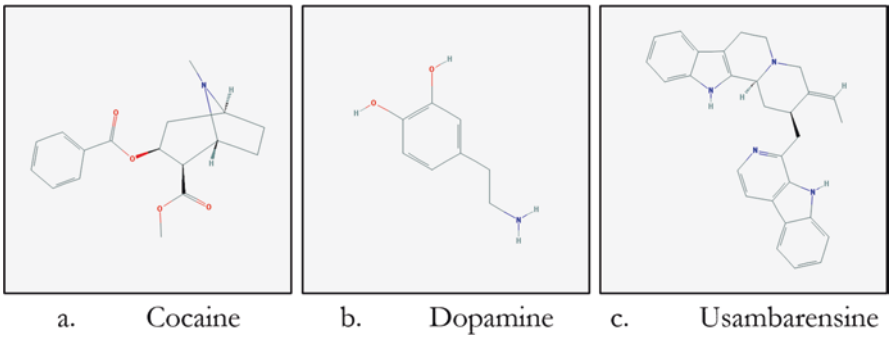

Fig. 5.2 Chemical structures of some of the most famous "true alkaloids." (**a**) Cocaine, (**b**) dopamine, (**c**) usambarensine

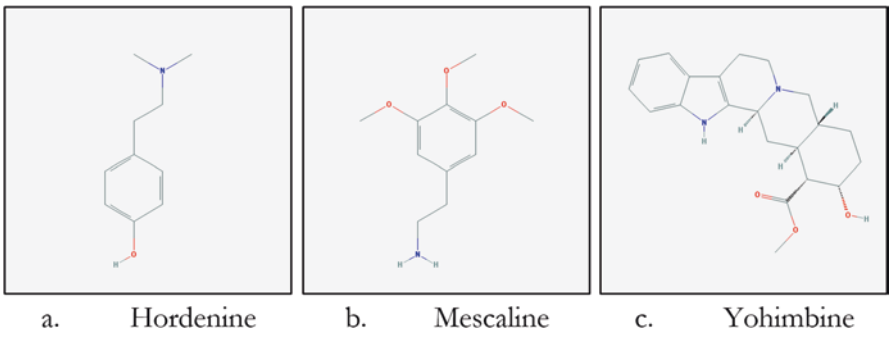

Fig. 5.3 Chemical structures of some of the most famous "protoalkaloids." (**a**) Hordenine, (**b**) mescaline, (**c**) yohimbine

Pseudoalkaloids are compounds whose carbon skeleton doesn't derive directly from amino acids (Jakubke et al. 1994) but from their precursors and postcursors (derivatives in the degradation process), from their amination or transamination reactions (Dewick 2002), or from non-amino acid precursor. The N atom can be donated at a relatively late stage in the case of steroidal or terpenoid skeletons or across a transamination reaction from an amino acid source in case of presence of a suitable aldehyde or ketone. Good examples of such kind of alkaloids are coniine, capsaicin, ephedrine, solanidine, caffeine, theobromine, and pinidine (Fig. 5.4).

Alkaloids occur abundantly in higher plants, and at least 25% of them contain alkaloids. Alkaloids are also contained in a larger number of plant species; however since the low alkaloid concentration is unable to influence cellular processes, such plants are not considered alkaloid species; alkaloids plants have been defined by Hegnauer (1966, 1967) as those plants containing more than 0,01% of alkaloids. Considering also the presence of slight traces, alkaloid plant families are the following:

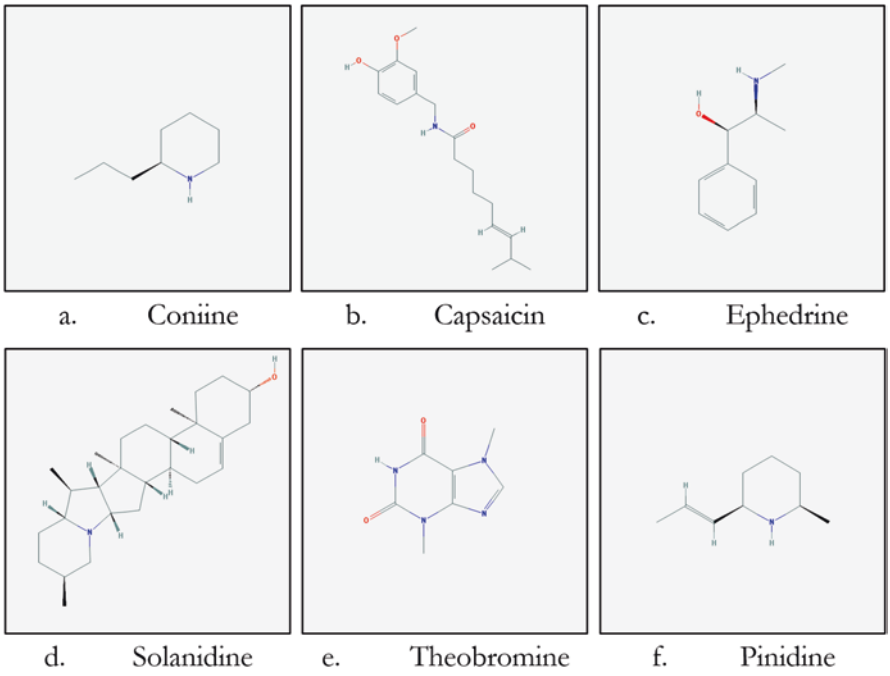

Fig. 5.4 Chemical structures of some of the most famous "pseudoalkaloids." (**a**) Coniine, (**b**) capsaicin, (**c**) ephedrine, (**d**) solanidine, (**e**) theobromine, (**f**) pinidine

- *Apocynaceae*: This family is also known as Dogbane botanical family and contains 150 genera and 1700 species, all particularly rich in L-tryptophan-derived alkaloids having a strong biological and medicinal effect and largely used in cancer chemotherapy (Aniszewski 2007). Typical examples of alkaloids belonging to such species are reserpine and rescinnamine, quinine, ibogaine, deserpine (Varchi et al. 2005), ervatine, tabersonine, coronaridine (Srivastava et al. 2001), and menilamine (Macabeo et al. 2005).
- *Asteraceae*: With 900 genera and more than 2000 species, this family results to be one of the largest and contains many different L-ornithine- and L-tryptophan-derived alkaloids. The most common alkaloids produced by the plants of this family are retrosine, senecionine (Pelser et al. 2005), apigenin (Aniszewski 2007), intergerrimine, and usaramine (Roeder et al. 1996).
- *Loganiaceae*: This family contains 30 genera and more than 500 species containing mainly L-tyrosine-derived biologically and medicinally very important alkaloids such as strychnine, brucine, curare, sungucine, isosungucine (Lansiaux et al. 2002), and isostrychnopentamine (Frédérich et al. 2004).
- *Papaveraceae*: Poppy botanical family contains 26 genera and about 250 plant species which produce many L-tyrosine-derived alkaloids, most of them having

a strong impact on biology and medicine such as morphine, codeine, thebanine, papaverine, narcotine, narceine, isoboldine, salsolinol (Aniszewski 2007), sanguinarine, cholidonine, hydrastine, berberine and chelerythine (Vavrečková et al. 1996a, b).

- *Rutaceae*: This family contains more than 150 genera and 900 species, many of them containing both L-anthranilic acid and L-histidine-derived alkaloids. Alkaloids derived from L-anthranilic acid include alkaloids such as dictamine, skimmianine, acronycine, melicopicine, rutacridone, acutine, acetylfolifidine, bucharidine, dubinidine, dubinine, glycoperine, evoxine, γ- fagarine, folifidine, foliosidine, haplophyline, haplopine, perfamine, skimmianine, helietidine, flindrsine, kokusaginine, and maculasine (Nazrullaev et al. 2001; de Moura et al. 2002). Some of the most famous L-histidine-derived alkaloids are instead represented by pilocarpine, pilosine, fagaronine, isodecarpine, 8-demethyloxychelerythine, 1-hydroxyrutaecarpine, rutaecarpine, 1-methoxyrutaecarpine, hyemaline, melicarpine, samecarpine, galipine, cusparine, cuspareine, demethoxycusparine, galipinine, evocarpine, dihydroevocarpine, and evodiamine (Sheen et al. 1996; Rakotoson et al. 1998; Shin et al. 1998; de Moura et al. 2002; Chen et al. 2003, 2005a).
- *Solanaceae*: It is a family consisting of 90 genera and more than 2000 species abundant in L-ornithine-derived alkaloids such as hyoscyamine, hyoscine, and cuscohygrine, nicotinic acid-derived alkaloids such as nicotine and anabasine, L-phenylalanine-derived alkaloids such as capsaicin, and steroidal-derived alkaloids such as solanidine, solamargine, solasodine, and tomatine (Schwarz et al. 2005).
- *Erythroxylaceae*: This family is also known as the coca plant family and contains a lot of L-ornithine-derived alkaloids commonly used in medicine and also in criminal activity such as cocaine, ecgonine, cinnamylcocaine, α-truxilline, truxilline, methylecgonine, tropine, hygrine, hygroline, and cuscohygrine (Aniszewski 2007).
- *Boraginaceae*: Includes 95 genera and about 2000 species rich in L-ornithine-derived alkaloids such as indicine-*N*-oxide, europine, and ilamine and their N-oxides, which have particularly strong toxic effects (Farsam et al. 2000), and several pyrrolizidine alkaloids used in local folk medicine as a diuretic, analgesic, sedative, and sudorific remedies, against stomach ulcers, and for treatment of skin diseases (Roeder 1995; Al-Douri 2000; Haberer et al. 2002; Said et al. 2002; Bracca et al. 2003; Siciliano et al. 2005).
- *Fabaceae*: This is one of the three largest families, including 650 genera and 18,000 species which contain mostly L-lysine-derived alkaloids such as lupinine, luparine, angustifoline, epi-lupanine, anagyrine, swainsonine, castanospermine, and many others (Przybylak et al. 2005), L-ornithine-derived alkaloids such as senecionine, and L-tryptophan-derived alkaloids such as eserine, eseramine,

physovenine, geneserine, erysovine, wrythraline, erysodine, α-erythroidine, β-erythroidine, dihydro-β-erythroidine, and many others, all of them biologically and ecologically significant (Soto-Hernandez and Jackson 1993; Lou et al. 2001; Tanaka et al. 2001; Wanjala et al. 2002; Kramell et al. 2005).

- *Menispermaceae*: Consists of 70 genera and 450 species which produce many L-tyrosine-derived alkaloids with medicinal effects or other activities that influence cellular processes such as tetrandrine, stephanine, curare, tubocurarine, methylliriodendronine, 2-*O*,*N*-dimetylliriodendronine, liriodenine, dicentronine, corydine, aloe-emodin, liriodenine, corydine, isocorydine, atherospermidine, stephalagine, dehydrostephalagine, stephalonines A–I, norprostephabyssine, isoprostephabyssine, isolonganone and isostephaboline, cepharathine, cepharanoline, isotetrandrine, and berbamine (Nakaoji et al. 1997; Camacho et al. 2000; Gören et al. 2003; Chen et al. 2005b).
- *Berberidaceae*: This family includes 10 genera and 574 species which produce L-tyrosine-derived alkaloids such as berberine, glaucine, hydroxyacanthin, and berbamine widely used in Japanese folk medicine against whooping cough, asthma, pharynx tumors, uterine bleeding, and diabetes and also as antiarrythmic, anti-myocardial, anti-ischemic, and antithrombotic (Khamidov et al. 2003; Orallo 2004; Aniszewski 2007).
- *Ranunculaceae*: A family consisting of about 2000 species distributed in 50 genera and producing L-tyrosine-derived alkaloids such as berberine, hydrastine, fangcholine, and fuzitine (Erdemgil et al. 2000) and terpenoid-derived alkaloids such as aconitine, sinomontanine, karacoline, karakanine, songorine, nepelline, 12-acetylnepelline, cammaconine, secokaraconitine (Tashkhodzhaev et al. 2000; Sultankhodzaev et al. 2002) tangutisine, acorone, acorridine, coryphine, coryphidine (Dzhakhangirov and Bessonova 2002), methyllycaconitine, barbine, delcorinine, delsonine (Salimov 2001), lycoctonine, anthranoyllycoctonine, ajacine, and delpoline (Boronova and Sultankhodzhaev 2000).
- *Liliaceae*: With more than 200 genera and around 3500 species, it is a very large family of plant, most of them producing L-tyrosine-derived alkaloids such as autumnaline, floramultine, kreysigin, and the well-known colchicine (Aniszewski 2007) and steroidal alkaloids such as jervine, cyclopamine, cycloposine, protoveratrine A and protoveratrine B, and *O*-acetyljervine used in Chinese folk medicine as antitussive and expectorant (Suladze and Vachnadze 2002; Jiang et al. 2005).
- *Rubiaceae*: Plants of this family are included in 400 genera and 6000 species producing adenine-/guanine-derived alkaloids, also called purine-derived alkaloids, such as caffeine, theophylline, and theobromine, leading to a positive and prophylactic effect against Parkinson's disease (Aniszewski 2007), L-tryptophan-derived alkaloids such as walterione A (Hoelzel et al. 2005), corynantheidine, corynantheine, dihydrocorynantheine, α-yohimbine, corynanthine, quinine, quinidine, cinchonine, cinchonidine, and many other molecules with biological and ecological important effects (Staerk et al. 2000; Ravishankara et al. 2001; Horie et al. 2005; Matsumoto et al. 2005).

- *Amaryllidaceae*: This family comprises of 50 genera including more than 850 plant species which produce L-tyrosine-derived alkaloids such as lycorine, galanthamine, galanthindole, galanthine, haemanthamine, lycorine, lycorenine, oxomaritidine, maritidine, vittatine, and many other molecules provided the different and important biological activities (Antoun et al. 1993; Bastida et al. 1996a, b; Machocho et al. 1998; Lewis, 1999; Unver et al. 1999; Lewis 2000; Herrera et al. 2001; Abou-Donia et al. 2002; Unver et al. 2003; Szlávik et al. 2004; Forgo and Hohmann 2005).
- *Elaeagnaceae*: This family consists of 3 genera and 50 species which produce among the other the L-tryptophan-derived alkaloid eleagine (Aniszewski 2007).
- *Zygophyllaceae*: With around 30 genera and more than 230 species, this family includes plants containing the L-tryptophan-derived alkaloid known as harman, the anthranilic acid-derived alkaloids called harmine, and the acetate-derived alkaloids dihydroschoberine, nitrabirine N-oxide, komavine, and acetylkomavine (Tulyaganov and Allaberdiev 2001; Tulyaganov et al. 2001).

5.3 Biological and Pharmaceutical Properties of Alkaloids

Alkaloids are the oldest successfully used drugs throughout history in the treatment of many diseases, this for their biological activity that operates not only on the endogenous life processes in the organisms that produce them but also in the organisms that come in contact with them (Wink 1998). These compounds are nontoxic in vacuoles where they are stored but toxic when they get away in different cells and tissues, due to the change in chemical configurations according to pH changes; this implies that alkaloids can have different biological activities in different cell conditions and different receptors (Aniszewski 2007).

Alkaloids play a very important role in an organism's metabolism and functions; their biological activity can be very different and dependent on their chemical structure. These compounds are biologically significant as active stimulators, inhibitors, and terminators of growth or part of endogenous safety and regulation mechanisms. It has been hypothesized that alkaloids, in addition to having this pivotal role in plant metabolism, can also be considered as vegetable waste (Waller and Nowacki 1978).

As a matter of fact, alkaloids are the most important active compounds in natural herbs. The distributing effect on the nervous systems of animals of alkaloids is widely known, among which is the analgesic action of morphine (Benyhe 1994). Some of them have also significance in the hemoglobinizators of leukemia cells, and they can be biologically determined to be estrogenically active molecules (Dupont et al. 2005). They display antimicrobial and antiparasitic properties (Fernandez et al. 2010; Cushnie et al. 2014). Recent research has proved that their biotoxicity is directed only toward foreign organisms or cells and is selective (Aniszewski 2007). Alkaloids can alter DNA, selectively deform cells, and cause locoism, a disease usually of horses, cattle, and sheep caused by chronic poisoning with locoweeds (plant that produces swainsonine, a phytotoxin harmful to

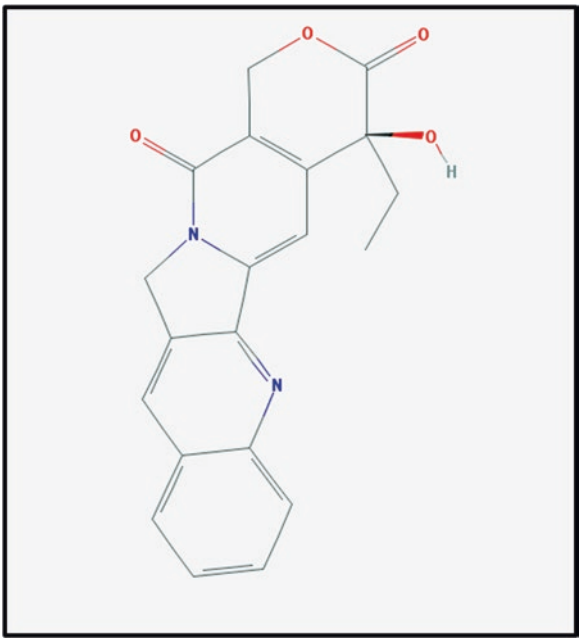

Fig. 5.5 Chemical structure of camptothecin

livestock) (Takanashi et al. 1980; Chenchen et al. 2014). Some alkaloid molecules, both natural and synthetic, can act as narcotics (Das and Ratty, 1987; Collins et al. 2002). Moreover, they play a very important role in the immune systems of animals and plants (Castellino et al. 2006). Several alkaloids demonstrate more important biological activities for treating asthma, such as the relieving action of ephedrine (Lee 2011), and last but not the least the anticancer activities of some compound as camptothecin (CPT), colchicine, and vinblastine (VBL) (Huang et al. 2007; Li et al. 2007; Ghawanmeh et al. 2018).

Some alkaloids have been successfully turned into chemotherapeutic drugs, and an example is camptothecin (CPT) (Fig. 5.5), a topoisomerase I inhibitor (Huang et al. 2007). This compound is a monoterpene indole alkaloid naturally extracted from the bark of *Camptotheca acuminata*, a tree used in traditional Chinese medicine for cancer treatment (Sadre et al. 2016). Wall et al. (1966) in systematic screening of natural products first demonstrated the high anticancer activity of CPT in preliminary clinical trials. The mode of action of CPT is the specific inactivation of topoisomerase I resulting in cell death by apoptosis (Wright et al. 2015).

Due of its low solubility and adverse drug reaction, derivatives to improve pharmacological properties and clinical efficacy have been synthesized, and two semisynthetic analogues, topotecan and irinotecan (Samuelsson, 2004), have been approved and used in cancer chemotherapy (Takimoto and Calvo 2008).

Another important alkaloid used for cancer therapy is colchicine (Fig. 5.6), a compound that promotes microtubule depolymerization (Ghawanmeh et al. 2018). Colchicine is originally extracted from plants of the genus *Colchicum* (*Colchicum*

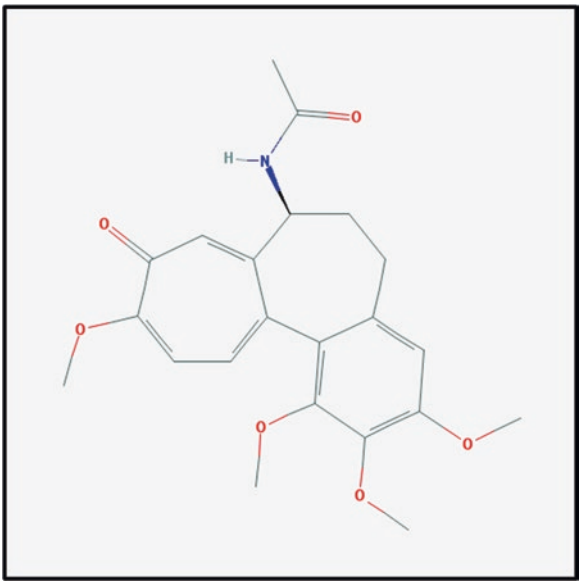

Fig. 5.6 Chemical structure of colchicine

autumnale) and was first isolated in 1820 by two French chemists, Pelletier and Caventou. This compound is known in the treatment of different diseases (Dasgeb et al. 2018), such as gout (Dalbeth et al. 2014) and rheumatism (Slobodnick et al. 2018).

The mechanism of action of colchicine is to bind to tubulin, blocking the microtubule polymerization. The pivotal role of microtubules in various cellular processes classifies colchicine as an antimitotic drug, by forming tubulin-colchicine complexes in a reversible manner and preventing the elongation of the microtubule polymer (Leung et al. 2015).

Probably the most famous alkaloids used for cancer therapy are vinblastine (VBL) and vincristine (VCR) (Fig. 5.7). These two compounds are bisindole alkaloids that consist of two subunits, an upper catharanthine ring system linked to a lower vindoline ring system by a single bond (Kingston 2009), and are the first plant-derived natural products used in the clinical field for cancer treatment (Lukesh et al. 2017). These compounds are extracted from the leaves of the Madagascar periwinkle *Catharanthus roseus* (L.), also called *Vinca rosea* (Kingston 2009), and have been discovered in the 1950s by the Canadian scientists Noble and Beer (Moudi et al. 2013).

The Vinca alkaloids have been also used to treat diseases such as diabetes and high blood pressure (Moudi et al. 2013). These compounds belong to the class of antimicrotubular antiblasts; microtubules are components of the cytoskeleton and play important roles in eukaryotic cellular functions such as intracellular organelle transport, cell migration, cell signalling, and mitosis (Perez 2009). The mechanism of action of vinblastine and vincristine is to prevent the polymerization of microtubules by the interaction with the β-subunit of tubulin during the formation of the mitotic spindle, causing cell metaphase arrest (Himes 1991; Li et al. 2007).

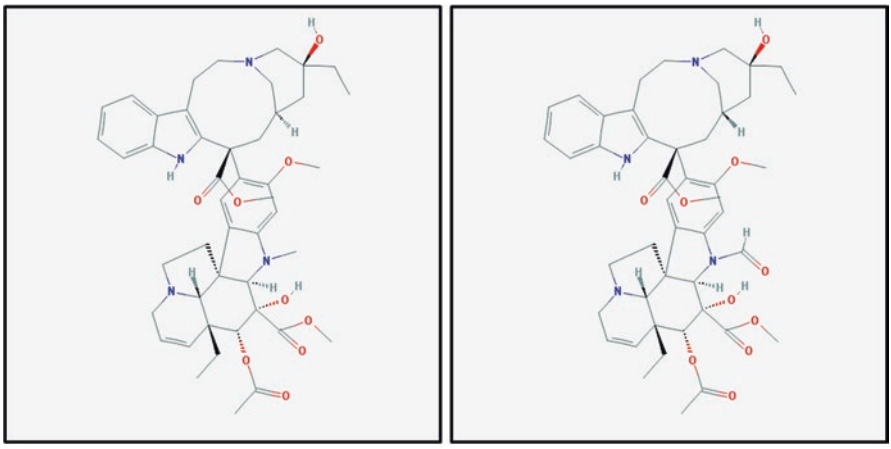

Fig. 5.7 Chemical structure of vinblastine (**a**) and vincristine (**b**)

This phenomenon contributes to reduce the number of cancer cells. Both VBL and VCR are efficacious clinical drugs used in combination therapies to treat Hodgkin's disease; testicular, ovarian, breast, head, and neck cancer; and non-Hodgkin's lymphoma or in the curative treatment regimens for childhood lymphocytic leukemia. VBL has some side effects to white blood cells and can induce patients' problems such as nausea, vomiting, constipation, dyspnea, chest or tumor pain, wheezing, and fever and is rarely associated with antidiuretic hormone secretion (Rowinsky 2003).

Presently four major Vinca alkaloids are in clinical use: vinblastine (VBL), vincristine (VCR), vinorelbine (VRL), and vindesine (VDS); only VCR, VBL, and VRL are approved for use in the United States (Rowinsky 2003).

Different synthetic Vinca alkaloids were produced in the last few years: vinflunine that is currently approved in Europe for medicinal treatment (Bennouna et al. 2008; Schutz et al. 2011) and vindesine that was the first analogue of VBL entered in clinical use.

Vindesine (Fig. 5.8), unlike VBL, has an amide function rather than a methyl ester on the vindoline ring and does not have an acetyl group on this ring system. It has higher hematological toxicity than vincristine, but it has been incorporated into several effective combination regimens for treatment of leukemia, lymphoma, and non-small cell lung cancer (NSCLC) (Dancey and Steward 1995; Joel 1996; Butler 2005).

Moreover vinorelbine (Fig. 5.9), a semi-synthetic derivative of VBL in which the bridge linking the indole ring to the piperidine nitrogen has been shortened by one carbon and water has been eliminated from the piperidine ring (Clardy and Walsh 2004), was launched in 1989 for the treatment of non-metastatic breast cancer and NSCLC (Mano 2006; Gralla et al. 2007).

Recently, a new synthetic Vinca alkaloid was produced: vinflunine, developed through the addition of two fluor elements by superacidic chemistry (Fig. 5.10). This molecule is the first fluorinated microtubule inhibitor that belongs to the

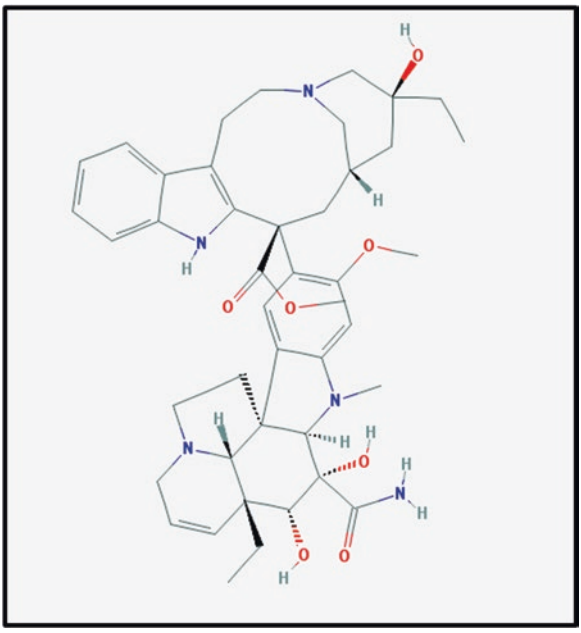

Fig. 5.8 Chemical structure of vindesine

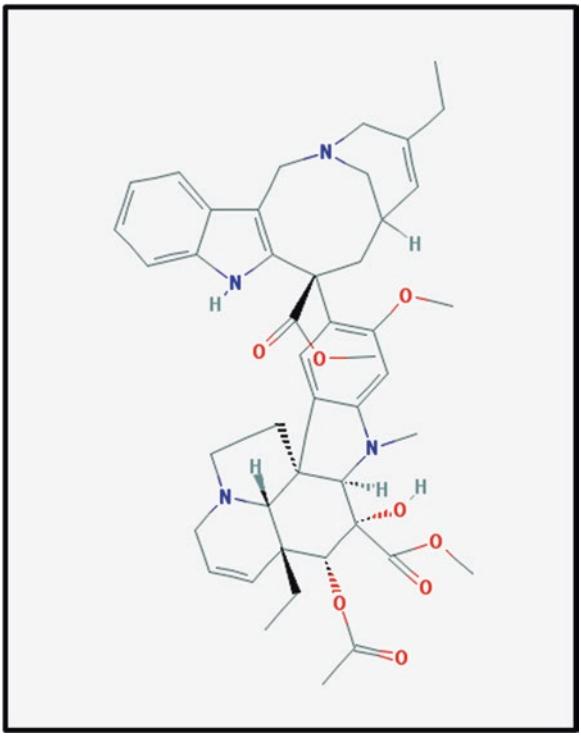

Fig. 5.9 Chemical structure of vinorelbine

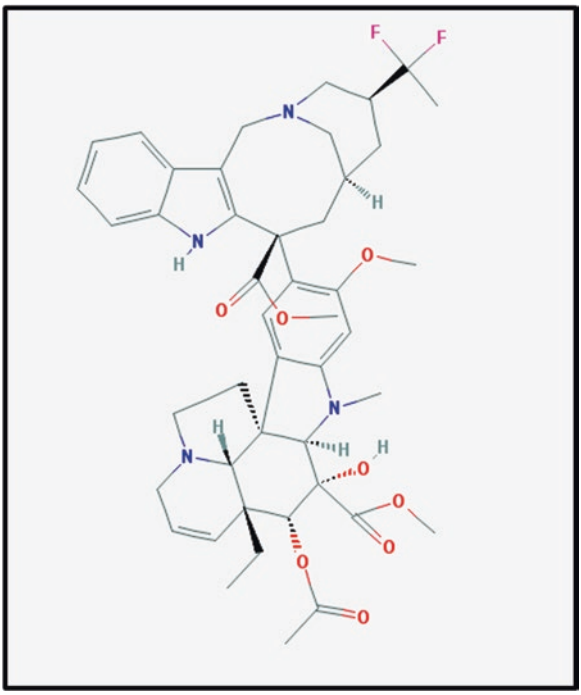

Fig. 5.10 Chemical structure of vinflunine

Vinca alkaloids, and it has been used in Europe for the treatment of second-line transitional cell carcinoma of the urothelium (TCCU). Furthermore, it has been applied for clinical development in a wide spectrum of solid tumors, and important activity has been observed in the treatment of transitional cell carcinoma of the urothelial tract, non-small cell lung cancer, and breast carcinoma. Vinflunine has been also tested in patients with TCCU and first-line advanced breast cancer (Moudi et al. 2013).

Anhydrovinblastine (Hydravin™, KRX-0403, 6) is an analogue of vinblastine that differs from its parent by one molecule of water. It can also be considered a homologue of vinorelbine with an additional carbon in the indole-piperidine bridge (Fig. 5.11). It entered phase I trial for the treatment of advanced solid tumors, including NSCLC, soft tissue sarcoma, and colorectal cancer (Lu et al. 2012; Moudi et al. 2013).

Other alkaloids of plant origin were investigated for anticancer activities. For instance, homoharringtonine (HHT) is an alkaloid with a cephalotaxine nucleus. It was first isolated from *Cephalotaxus harringtonii* and *Cephalotaxus fortunei* trees, whose bark extracts were used in Chinese traditional medicine to treat cancer. Homoharringtonine and other cephalotaxine derivatives can also be found in leaves, bark, and seeds of other *Cephalotaxus* species (Kantarjian et al. 2013). The cephalotaxine itself is very abundant in *Cephalotaxus* species leaves, which can be isolated and transformed by simple esterification into homoharringtonine. Since the

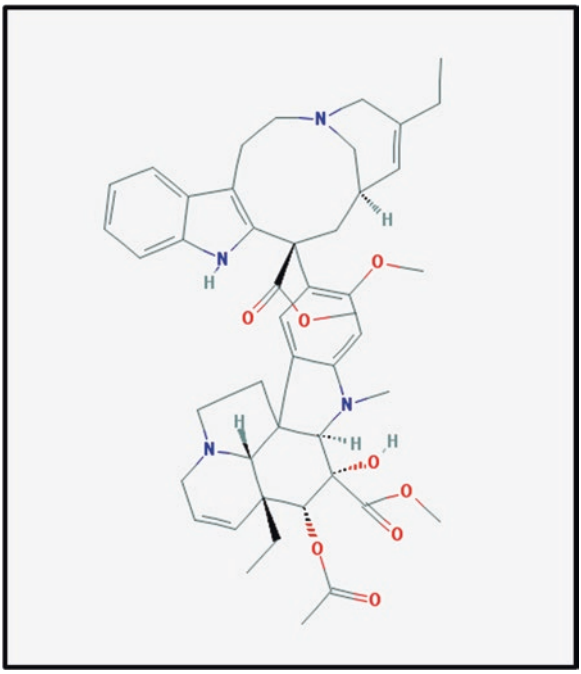

Fig. 5.11 Chemical structure of anhydrovinblastine

1970s, homoharringtonine or a mixture of cephalotaxus esters have been used in China to treat hematological malignancies (Lü and Wang 2014).

Homoharringtonine is a protein translation inhibitor, and its mechanism of action consists in the inhibition of the elongation step of protein synthesis. It binds to the A-site of the large ribosomal subunit, and this action blocks the access of the charged tRNA and consequently the peptide bond formation. Its success is mainly due to the fact that it can perturb proteins with rapid turnover such as the leukemic cell upregulated short-lived oncoproteins BCR-ABL1 and antiapoptotic proteins (Mcl-1, Myc) leading to cells apoptosis (Gandhi et al. 2014). Homoharringtonine, also called omacetaxine mepesuccinate (Fig. 5.12), was approved by FDA in 2012 (sold under the trade name Synribo®) and used in the treatment of chronic myeloid leukemia in patients with resistance and/or intolerance to two or more tyrosine kinase inhibitors; it is the only natural therapeutic agent approved as a commercial drug to treat chronic myeloid leukemia (Seca and Pinto 2018).

Berberine (Fig. 5.13) is an isoquinoline alkaloid extensively distributed in natural herbs (Chen et al. 2008) with a variety of biological activities such as anti-inflammatory, antibacterial, antidiabetes, antiulcer, sedation, protection of myocardial ischemia-reperfusion injury, expansion of blood vessels, inhibition of platelet aggregation, and hepatoprotective and neuroprotective effects (Lau et al. 2001; Yu et al. 2005; Han et al. 2010; Ji 2011). Studies have demonstrated that berberine possesses anticancer potentials by interfering with tumorigenesis and tumor progression in both in vitro and in vivo experiments (Sun et al. 2009; Diogo

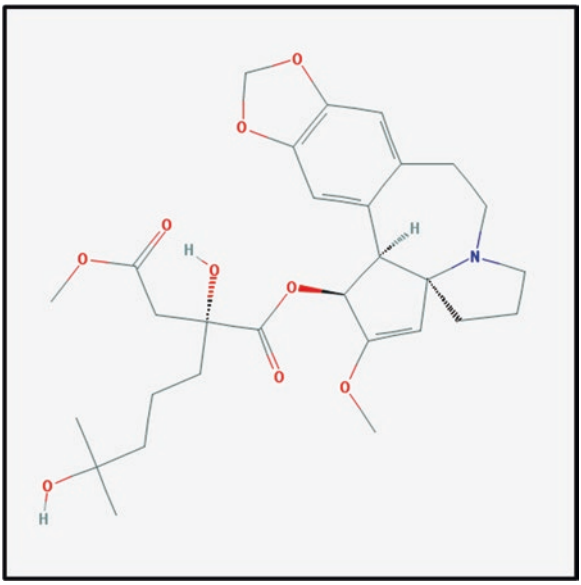

Fig. 5.12 Chemical structure of homoharringtonine also named omacetaxine mepesuccinate

et al. 2011; Tan et al. 2011). Berberine inhibits the proliferation of multiple cancer cell lines by inducing cell cycle arrest at G1 or G2/M phases and by apoptosis (Sun et al. 2009; Eom et al. 2010; Burgeiro et al. 2011) and endoplasmic reticulum stress (Eom et al. 2010) and autophagy (Wang et al. 2010) in cancer cells. Moreover, its combination with chemotherapeutic drugs or irradiation could enhance the therapeutic effects (Youn et al. 2008; Hur et al. 2009). Other mechanisms of berberine are mainly related to its effect on cell cycle arrest and apoptosis, including regulation of cyclin-dependent kinase (CDK) family of proteins (Mantena et al. 2006; Sun et al. 2009) and expression regulation of B-cell lymphoma 2 (Bcl-2) family of proteins (such as Bax, Bcl-2, and Bcl-xL) (Mantena et al. 2006; Sun et al. 2009; Eom et al. 2010) and caspases (Mantena et al. 2006; Eom et al. 2010). Furthermore, berberine inhibits the activation of the nuclear factor κ-light-chain enhancer of activated B cells (NF-κB) and promotes the formation of intracellular reactive oxygen species (ROS) in cancer cells (Sun et al. 2009; Eom et al. 2010).

Evodiamine (Fig. 5.14), a quinolone alkaloid, is one of the major bioactive compounds extracted from the Chinese herb *Evodia rutaecarpa*; this molecule exhibits anti-inflammatory, antiallergic, anti-obese, and anticancer effects. Anticancer activities were reported both in vitro and in vivo. Its mechanism of action is inducing cell cycle arrest or apoptosis, and it can inhibit angiogenesis, invasion, and metastasis in a variety of cancer cell lines (Ogasawara et al. 2001, 2002; Fei et al. 2003; Zhang et al. 2003; Shyu et al. 2006). Evodiamine also stimulates autophagy, a physiological process involved in the maintenance of cell homeostasis (Yang et al. 2008). Compared with other compounds, evodiamine is less toxic toward normal human cells, such as human peripheral blood mononuclear cells.

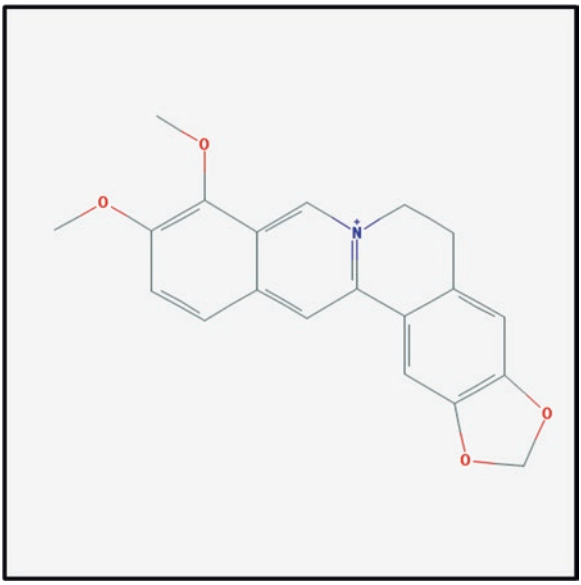

Fig. 5.13 Chemical structure of berberine

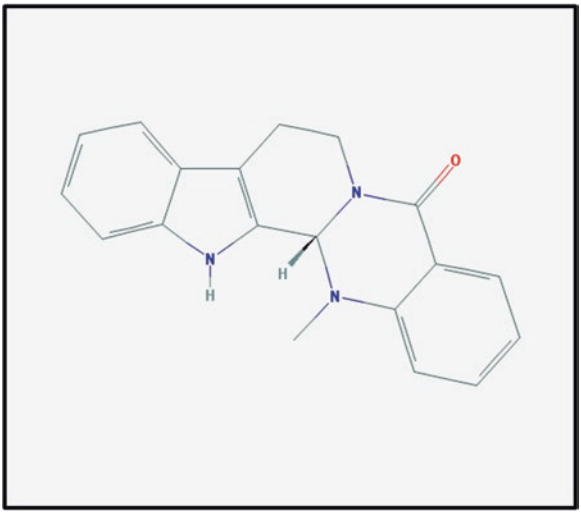

Fig. 5.14 Chemical structure of evodiamine

Matrine (Fig. 5.15) is a major alkaloid found in many *Sophora* plants, including *Sophora flavescens* Ait. (Lai et al. 2003). It exhibits a wide range of pharmacological properties such as antibacterial, antiviral, anti-inflammatory, antiasthmatic, antiarrhythmic, anti-obesity, cardioprotective effects, diuretic, choleretic, hepatoprotective, nephroprotective, and anticancer (Long et al. 2004; Zhang et al. 2007; Zheng et al. 2009; Han et al. 2010; Li et al. 2010; Xing et al. 2010; Zhang et al. 2011a, b). It inhibits the proliferation of various types of cancer cells mainly through

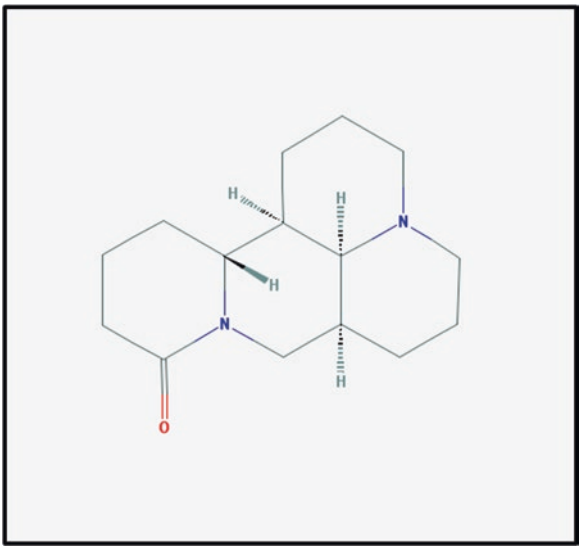

Fig. 5.15 Chemical structure of matrine

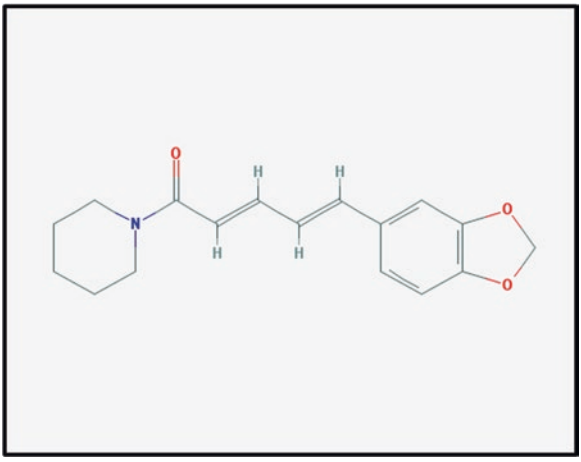

Fig. 5.16 Chemical structure of piperine

mediation of G1 cell cycle arrest or apoptosis (Jiang et al. 2007; Dai et al. 2009; Liu et al. 2010; Zhang et al. 2011a, b, 2012). It inhibits cancer cell invasion partially throughout the inhibition of MMP-2 and MMP-9 expression and modulation of the NF-κB signalling pathway (Yu et al. 2009; Luo et al. 2011; Yu et al. 2011).

Piperine (Fig. 5.16), a piperidine alkaloid isolated from *Piper nigrum* (also known as black pepper) and *Piper longum*, two famous spices that have been used for centuries (Szallasi 2005), exhibits antioxidant, anti-inflammatory, antidiarrheal, anticonvulsant, antimutagenic, and hypolipidemic effects, promoting bile secretion and tumor-inhibitory activities (Srinivasan 2007; Ji 2011; Bae et al. 2010). The che-

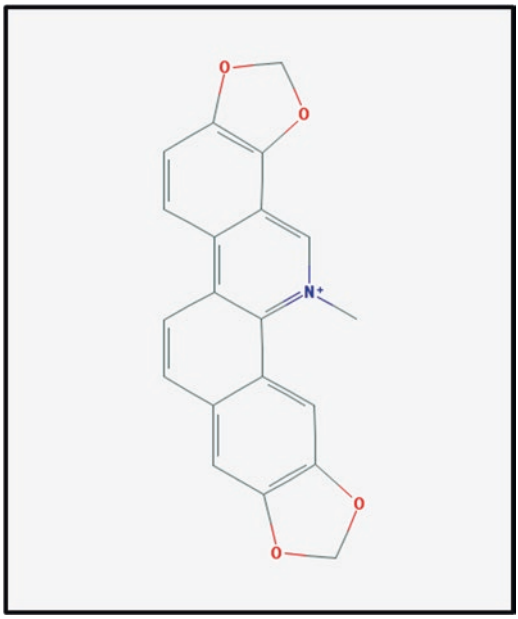

Fig. 5.17 Chemical structure of sanguinarine

mopreventive effects of piperine against several kinds of carcinogen, such as benzo(a)pyrene and 7,12-dimethyl benz(a)anthracene, show its potential as a cancer preventive agent (Khajuria et al. 1998; Selvendiran et al. 2003, 2005a, b; Selvendiran and Sakthisekaran 2004; Krishnakumar et al. 2009; Manoharan et al. 2009). A recent study has shown that piperine inhibits breast stem cell self-renewal and does not cause toxicity to differentiated cells (Kakarala et al. 2010).

Sanguinarine (Fig. 5.17) is a benzophenanthridine alkaloid isolated from the Papaveraceae family, which includes *Sanguinaria canadensis* L. (also known as bloodroot) and *Chelidonium majus* L. (Mahady and Beecher 1994; Vavrečková et al. 1996a, b). It has antibacterial, antifungal, antischistosomal, antiplatelet, anti-inflammatory (Lenfeld et al. 1981; Beuria et al. 2005; Jeng et al. 2007; Ji 2011), and also anticancer potentials (Debiton et al. 2003; Ahsan et al. 2007; Chang et al. 2007; Hussain et al. 2007). Sanguinarine induces cell cycle arrest at different phases or apoptosis in a variety of cancer cells lines (Adhami et al. 2003, 2004; Ahsan et al. 2007; Chang et al. 2007; Hussain et al. 2007; Kim et al. 2008). It remarkably sensitizes breast cancer cells to tumor necrosis factor-related apoptosis inducing ligand-mediated apoptosis (Kim et al. 2008). Sanguinarine also shows antiangiogenic effects in mice (5 mg/kg), presents anti-invasive effects, and overcomes P-gp-mediated MDR phenotype (Weerasinghe et al. 2006; De Stefano et al. 2009; Choi et al. 2009). Sanguinarine is a selective inhibitor of mitogen-activated protein kinase phosphatase 1 (MKP-1), which is overexpressed in many tumor cells (Vogt et al. 2005). Commercial uses of sanguinarine and bloodroot extract consist of dental hygiene products. FDA has approved the inclusion of sanguinarine in toothpastes as an antibacterial or anti-plaque agent (Kuftinec et al. 1990).

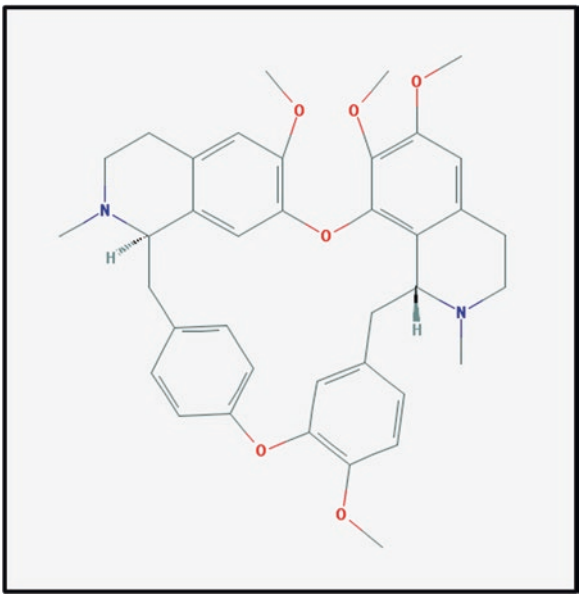

Fig. 5.18 Chemical structure of tetrandrine

Tetrandrine (Fig. 5.18), a bisbenzylisoquinoline alkaloid from the root of *Stephania tetrandra*, exhibits a broad range of pharmacological activities including immunomodulating, antihepatofibrogenetic, anti-inflammatory, antiarrhythmic, antiportal hypertension, anticancer, and neuroprotective activities (Li et al. 2001; Ji 2011). Tetrandrine induces cell cycle arrest (Kuo and Lin 2003; Meng et al. 2004; Ng et al. 2006) and apoptosis in many human cancer cells, including leukemia, bladder, colon, hepatoma, and lung (Lai et al.1998; Lee et al. 2002; Yoo et al. 2002; Kuo and Lin, 2003; Meng et al. 2004; Ng et al. 2006; Wu et al. 2010; Li et al. 2011; He et al. 2011). Co-administration of tetrandrine restores the sensitivity of MDR cancer cells to doxorubicin, paclitaxel, docetaxel, and vincristine (Fu et al. 2002, 2004; Zhu et al. 2005) through the inhibition of P-gp.

5.4 Conclusion

Since their discovery, alkaloids have had many applications as helpful pharmaceutical tools against pathologies, and investigations are running in labs to discover new alkaloid molecules and characterize their potential biological properties. In recent time the increasing of chemical investigations on natural compounds allowed to better understand on pharmaceutical potentialities of alkaloids and their derivates and by such molecules perspectives are now open for a more detailed characterization of cellular pathways and new useful applications in medicine.

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