Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

—CHAPTER 1—

ALLELOCHEMICAL PROPERTIES OR THE RAISON D'ÊTRE OF ALKALOIDS

MICHAEL WINK

Universität Heidelberg
Institut für Pharmazeutische Biologie
6900 Heidelberg, Germany

I. Introduction 1
II. Allelochemical Properties of Alkaloids 5
A. Plant–Herbivore Interactions 8
B. Plant–Microbe Interactions 61
C. Antiviral Properties 79
D. Allelopathic Properties 82
III. Raison d'Être of Alkaloids 86
A. Concentrations in Plants and Allelochemical Activities 87
B. Presence of Alkaloids at the Right Site and Right Time 89
C. Importance of Alkaloids for Fitness of Plants 92
D. Exceptions to the Rule: Role of Adapted Specialists 96
IV. Conclusions 103
References 104

I. Introduction

Plants constitute the major group of photoautotrophic organisms on our planet that are able to use solar energy to fix carbon dioxide into hydrocarbons, such as glucose, and to produce ATP and $NADPH_2$ as "fuel" and reduction equivalents, which serve to build up all the other essential components of a cell. Animals and most microorganisms (except the chemo- or photoautotrophic bacteria) are heterotrophic organisms, which rely on complex, plant-made organic molecules for their energy requirement or other metabolic functions. Thus plants serve as a major and ultimate source of food for animals and microorgansims, whether they like it or not.

We can safely assume that plants struggle for life and that they have evolved strategies against herbivorous animals or phytopathogenic micro-

THE ALKALOIDS, VOL. 43

organisms. We must also consider that plants compete with other plants (of the same or different species) for light, water, and nutrients.

How do plants defend themselves against microorganisms (including bacteria, fungi, and viruses), herbivores, and plants? Because plants do rather well in Nature, this question has often been overlooked. We are well aware of the defensive strategies of higher animals against microbes and predators (*1,2,4,15,17,28,494*). The complex immune system with its cellular and humoral components is a well-studied area in the context of vertebrate–microbe interactions. Against predating animals, Nature evolved weapons, armor, crypsis, thanatosis, deimatic behavior, aposematism, flight, or defense chemicals (usually called "poisons") (*1*).

It is evident that most of these possibilities are not available for plants with their sessile and "passive" life-style. What then is their evolutionary solution? We can distinguish the following defense mechanisms in plants (*3,4,7,15,17*); the mechanisms are not independent and may act cooperatively and synergistically. We should be aware that many species have additionally evolved specialized traits in this context.

1. Mechanical protection is provided by thorns, spikes, trichomes, glandular hairs, and stinging hairs (which are often supported by defense chemicals).
2. Formation of a thick bark on roots and stems can be considered as a sort of armor, and the presence of hydrophobic cuticular layers as a penetration barrier directed against microbes.
3. If plants are wounded or if parts of them are eaten, this is usually not as fatal as the similar situation in animals, since plants can easily replace a lost leaf or branch (so-called open growth).
4. A most important strategy, however, is the production and storage of defense chemicals, which are abundant and a typical trait of all plants.
   a. Plant surfaces are usually covered by a hydrophobic layer consisting of antibiotic and deterrant/repellent cuticular waxes which may contain other biologically active allelochemicals such as flavonoids (*3–5,7*).
   b. Cell walls are biochemically rather inert with reduced digestibility to many organisms because of their complex cellulose, pectin, and lignin molecules. Callose and lignin are often accumulated at the site of infection or wounding (*6,7*) and form a penetration barrier.
   c. Synthesis of inhibitory proteins (e.g., lectins, protease inhibitors) or enzymes (e.g., chitinase, lysozyme, hydrolases, nucleases) that could degrade microbial cell walls or other microbial constituents would be protective, as well as synthesis of peroxidase and phenolase, which could help inactivate phytotoxins produced by many bacteria and fungi. These proteins are either stored in the vacuole

or are secreted as exoenzymes into the cell wall or the extracellular space (*8,9*). These compounds are thus positioned at an "advanced and strategically important defense position." In addition, storage proteins (of cereals and legumes) are often deficient in particular essential amino acids, such as lysine or methionine.

d. As a widely distributed and important trait, secondary metabolites with deterrent/repellent or toxic properties against microorganisms, viruses, and/or herbivores may be produced (*2–4, 10–21*). These allelochemicals can be constitutively expressed, they may be activated by wounding (e.g., cyanogenic glycosides, glucosinolates, coumaryl glycosides, alliin, ranunculin), or their *de novo* synthesis may be induced by elicitors (so-called phytoalexins), infection, or herbivory (*4,7,22–24*). These products are often synthesized and stored at strategically important sites [epidermal tissues or in cells adjacent to an infection (*25,26*)] or in plant parts that are especially important for reproduction and survival [flowers, fruits, seeds, bark, roots (*2,3,15*)].

In animals, we can observe the analogous situation in that many insects and other invertebrates (especially those which are sessile and unprotected by armor), but also some vertebrates, store secondary metabolites for their defense which are often similar in structure to plant allelochemicals (*1,4,12,16,17,28–30,494–496,503*). In many instances, the animals have obtained the toxins from their host plants (*4, 12,15,17,27-33*). Hardly any zoologist or ecologist doubts that the principal function of these secondary metabolites (which are often termed "toxins" in this context) in animals is that of defense against predators or microorganisms (*1,17,28,494–496*).

These defense compounds are better known as natural products or secondary metabolites. The latter expression originally meant compounds which are not essential for life, and thus distinct from primary metabolites (*34,35,38*). Unfortunately the term "secondary" has also a pejorative meaning, indicating perhaps that the compounds have no importance for the plant. As discussed in this chapter, just the opposite is true.

More than 30,000 natural products have been reported from plants so far (*2,4,17*). Owing to the sophistication in phytochemical methods, such as chromatography (HPLC, GLC) and spectroscopy (NMR, MS), new products are reported at rapid intervals. Because only 5–10% of all higher plants, which consist of over 300,000 species, have been analyzed phytochemically in some detail, the overall real number of secondary products is certainly very large.

It is a common theme that an individual plant does not produce a single natural product, but usually a moderate number of major metabolites and a larger number of minor derivatives. Within a taxon secondary metabolites

often share a common distribution pattern and are therefore of some importance for phytochemical systematics. Classic taxonomy, however, has taken little account of alkaloid distribution: If the same alkaloid is present in two plants of the same taxon, this is interpreted as evidence for a relationship, but its occurrence in two plants of nonrelated taxa is taken as evidence of independent evolution. Because secondary metabolites are also derived characters that were selected during evolution, their general value for taxonomy and systematics is certainly smaller than formerly anticipated (*233*).

For many years, secondary metabolites were considered as waste products or otherwise functionless molecules, merely illustrating the biochemical virtuosity of Nature (*34,35*). In 1887 and 1888, Errera and Stahl (*92,308,504*) published the idea that natural products are used by plants for chemical defense against herbivores. Since the leading plant physiologists of that time were mostly anti-Darwinian, they were not willing to accept the defense argument, which was too much in line with the Darwinian concept. Therefore, this early defense concept was negated and remained forgotten for nearly 60 years. In 1959, Fraenkel (*10*) reopened the debate in a review article and presented new data supporting the view that secondary metabolites serve as chemical defense compounds against herbivores. During the next three decades this concept was improved experimentally, and we can summarize the present situation as follows (*2–4,11–22,54,210*).

Although the biological function of many plant-derived secondary metabolites has not been studied experimentally, it is now generally assumed that these compounds are important for the survival and fitness of a plant and that they are not useless waste products, as was suggested earlier in the twentieth century (*34,35*). In many instances, there remains a need to analyze whether a given compound is active against microorganisms (viruses, bacteria, fungi), against herbivores (molluscs, arthropods, vertebrates), or against competing plants (so-called allelopathy).

In some instances, additional functions are the attraction of pollinating or seed-dispersing animals, for example, by colored compounds such as betalains (within the Centrospermae), anthocyanins, carotenoids, and flavonoids or by fragrances such as terpenes, amines, and aldehydes (*15,17*). Physiological roles, such as UV protection [by flavonoids or coumarins (*4,17*)], nitrogen transport or storage (*14,36,37*), or photosynthesis (carotenoids), may be an additional function.

Allelochemicals are often not directed against a single organism, but generally against a variety of potential enemies, or they may combine the roles of both deterrents and attractants (e.g., anthocyanins and many essential oils can be attractants in flowers but are also insecticidal and

antimicrobial). Thus, many natural products have multiple functions, a fact which is easily overlooked since most scientists usually specialize on a narrow range of organisms (i.e., a microbiologist will usually not check whether an antibiotic alkaloid also deters the feeding of caterpillars). To understand all the interactions we need to adopt a holistic, that is, interdisciplinary, approach.

It might be argued that the defense hypothesis cannot be valid since most plants, even those with extremely poisonous metabolites (from the human point of view), are nevertheless attacked by pathogens and herbivores. However, we have to understand and accept that chemical defense is not an absolute process. Rather, it constitutes a general barrier which will be effective in most circumstances, that is, most potential enemies are repelled or deterred. Plants with allelochemicals at the same time represent an ecological niche for potential pathogens and herbivores. During evolution a few organisms have generally been successful in specializing toward that niche (i.e., in a particular toxic plant) in that they found a way to sequester the toxins or become immune to them (*14,15,32*). This is especially apparent in the largest class of animals, the insects (probably with several million species on earth), which are often highly host plant specific. The number of these "specialists" is exceedingly small for a given plant species as compared to the number of potential enemies that are present in the ecosystem. We can compare this situation with our immune system: It works against the majority of microorganisms but fails toward a few viruses, bacteria, fungi, and protozoa, which have overcome this defense barrier by clever strategies. Nobody would call the immune system and antibodies useless because of these few adapted specialists! We should adopt the same argument when we consider plants' defenses by secondary metabolites (*2*).

Since secondary metabolites have evolved in Nature as biologically active compounds with particular properties in other organisms, many of them are useful to mankind as pharmaceuticals, fragrances, flavors, colors, stimulants, or pesticides. In addition, many allelochemicals provide interesting lead structures that organic medicinal chemists can develop into new and more active compounds.

II. Allelochemical Properties of Alkaloids

About 20–30% of higher plants accumulate alkaloids (*505,506*). The incidence of alkaloid production varies between taxa to some degree; for example, about 60–70% of species of the Solanaceae and Apocynaceae are

alkaloidal, whereas other families contain few alkaloid-producing species. Some alkaloids have a wide distribution in Nature: caffeine occurs in the largest number of families, lycorine in the largest number of genera and berberine in the largest number of species. Alkaloids are not restricted to higher plants (although they are here most numerous); they are also present in club mosses (*Lycopodium*), horsetails (*Equisetum*), fungi, and animals such as marine worms (e.g., Nereidae), bryozoans, insects (e.g., Coccinellidae, Solenopsidae), amphibians (toads, frogs, salamanders), and fishes.

Alkaloids thus represent one of the largest groups of natural products, with over 10,000 known compounds at present, and they display an enormous variety of structures, which is due to the fact that several different precursors find their way into alkaloid skeletons, such as ornithine, lysine, phenylalanine, tyrosine, and tryptophan (*38–40*). In addition, part of the alkaloid molecule can be derived from other pathways, such as the terpenoid pathway, or from carbohydrates (*38–40*). Whereas the structure elucidation of alkaloids and the exploration of alkaloid biosynthetic pathways have always commanded much attention, there are relatively few experimental data on the ecological function of alkaloids. This is the more surprising since alkaloids are known for their toxic and pharmacological properties and many are potent pharmaceuticals.

Alkaloids were long considered to be waste products [even by eminent alkaloid researchers such as W. O. James and Kurt Mothes (*34,35, 505,526*)]. Because nitrogen is a limiting nutrient for most plants, a nitrogenous waste product would be *a priori* unlikely. The waste product argument probably came from animal physiology: Carnivorous animals take up relative large amounts of proteins and nucleic acids, containing more nitrogen than needed for metabolism, which is consequently eliminated as uric acid or urea. A similar situation or need, however, is not applicable for plants. In fact, many plants remobilize their nitrogenous natural products (including alkaloids) from senescing organs such as old leaves (*2,37,506*). If alkaloids were waste products, we would expect the opposite, namely, accumulation in old organs which are shed. On the other hand, the alkaloids produced by animals were never considered to be waste products by zoologists, but rather regarded as defense chemicals (*16,28,494–496*).

Thus, the more plausible hypothesis is that alkaloids of plants, microorganisms, and animals, like other allelochemicals, serve as defense compounds. This idea is intuitively straightforward, because many alkaloids are known as strong poisons for animals and *Homo sapiens*.

As a prerequisite for an alkaloid to serve as a chemical defense compound we should demand the following criteria. (1) The alkaloid should have significant effects against microbes and/or animals in bioassays.

(2) The compounds should be present in the plant at concentrations that are of the same order (or, better, even higher) as those determined in the bioassays. (3) The compound should be present in the plant at the right time and the right place. (4) Evidence should be provided that a particular compound is indeed important for the fitness of a plant.

Although more than 10,000 alkaloids are known, only few (~2–5%) have been analyzed for biochemical properties, and even fewer for their ecophysiological roles. In most phytochemical studies only the structures of alkaloids have been elucidated, so that often no information is available on their concentrations in the different parts and through the ontogenetic development of a plant, or on their biological activities.

Furthermore, the corresponding studies were usually designed to find useful medicinal or sometimes agricultural applications of alkaloids, not to elucidate their evolutionary or ecological functions. These objections have to be kept in mind, because an alkaloid is sometimes termed "inactive" in the literature, which usually means less active than a standard compound already established as a medicinal compound (such as penicillins in antimicrobial screenings). In many medicinal experiments relatively low doses are applied because of the toxic properties of many alkaloids. If the same compound would have been tested at relevant (which normally means elevated) concentrations that are present in the plant, an ecologically relevant activity might have been detected. Another restriction is that the activities of alkaloids have been tested with organisms that are sometimes irrelevant for plants but medicinally important. However, if a compound is active against *Escherichia coli*, it is likely that is is also active against other gram-negative and plant-relevant bacteria. Nevertheless, most of the data obtained in these studies (Tables I–VIII) provide important information which at present permits extrapolation to the function of alkaloids in plants.

In this chapter the focus is on the biological activity of alkaloids (the information available on the pharmacological properties of alkaloids is mostly excluded), and we try to discuss these data from an ecological perspective. In the following, the possible functions of alkaloids in plant–animal, plant–plant, and plant–microbe interactions are discussed in more detail.

It is nearly impossible to cover the literature exhaustively. Therefore, an overview of the allelochemical properties of alkaloids is presented. Because of the large amount of data (literature up to 1990 is included), the selection of examples must remain subjective to some degree. Nevertheless, the author would be grateful to receive information or publications about relevant omissions.

A. Plant–Herbivore Interactions

Because *Homo sapiens* and domestic animals are to some degree herbivores, a large body of empirical knowledge has accumulated on the toxic properties of alkaloids (Tables I through V) and alkaloid-containing plants. Previously, the toxic properties of alkaloids in vertebrates was part of the definition (as a common denominator) for this group of natural products (*38,39*). In the following, the toxic or adverse effects of alkaloids are separately discussed for invertebrates (mainly insects) and vertebrates.

1. Invertebrates

Among the invertebrates, insects have been extremely successful from the evolutionary point of view, and they form the largest class of organisms on our planet as far as the number of both individuals and species is concerned. Entomologists estimate that the number of insects is at least 1 million, but tropical rain forests may harbor up to 20–30 million species, many of which are still unknown and, owing to the fast extinction of this ecosystem, will probably also disappear without having been discovered and studied by scientists.

Most insects are herbivores, and adaptation to host plants and their chemistry is often very close and complex (*1,4,10,14,15,28–33, 494–496,503*). Whereas insects rely on plants for food, many plants need insects for pollination and seed dispersal. In the latter context we often find that plants attract insects by chemical means (colors, fragrances, sugars, amino acids). At the same time, other secondary metabolites are employed to discourage the feeding on flowers and seeds.

The close association between plants, especially the angiosperms, and insects evolved during the last 200 million years. Some scientists have called this phenomenon a "coevolutionary" process, but it has to be recalled that the associations seen today are not necessarily those in which the chemical interactions originally evolved (*18,505,506*). Applications of synthetic insecticides have shown that resistance to these new compounds can occur rapidly, sometimes encompassing only a dozen generations. Times can also be much longer. If plant species are introduced to a new continent or island, it usually takes a long time before new pathogens or herbivores become adapted and specialized to this new species. For example, *Lupinus polyphyllus* from North America has a number of specialized herbivores, but is rarely attacked by herbivores in Europe. This lupine left its enemies behind when it was transferred to Europe three centuries ago. About 10 years ago, however, the North American lupine aphid (*Macrosiphum albifrons*) was introduced to Europe accidentally. This aphid is specialized to alkaloid-rich lupines with lupanine as a major

alkaloid. At present, this aphid has spread over most of Europe and is now colonizing its former host, *L. polyphyllus* (*2,503*).

Insect herbivores can be divided into two large groups whose strategies with respect to the plant's defense chemistry differ substantially (*15*). The polyphagous species can exploit a wide range of host plants, whereas the mono-/oligophagous insects are often specialized on one or a small number of (often systematically related) hosts.

Polyphagous insects, namely, species which feed on a wide variety of food plants, are usually endowed with fantastic and powerful olfactory receptors (*501*) that allow the distinction between plants with high or low amounts of "toxins." The receptors also allow insects to ascertain the quality of the essential products present, such as lipids, proteins, or carbohydrates (*507*). These "generalists," as we can also call this subgroup of herbivores, are usually deterred from feeding on plants which store especially noxious metabolites and select those with less active ones (such as our crop species, where man has bred away many of the secondary metabolites that were originally present; see Table XI). Alternatively, they change host plants rapidly and thus avoid intoxication. In addition, most polyphagous species have evolved active detoxification mechanisms, such as microsomal oxidases and glutathione peroxidase, which lead to the rapid detoxification and elimination of dietary secondary products (*4,15,17,508*).

In contrast, mono- and oligophagous species often select their host plants with respect to the composition of the nutrients and secondary metabolites present. For these "specialists" the originally noxious defense compounds are often attractive feeding and oviposition stimulants. These insects either tolerate the natural products or, more often, actively sequester and exploit them for their own defense against predators or for other purposes (*1,4,10–12,14–17,28,31,33,494–496*). These observations seem to contradict the first statement, that secondary metabolites are primarily defense compounds, and a number of renowned authors have fallen into this logical pit, such as Mothes (*35*) and Robinson (*505*). However, these specialized insects are exceptions to the general rule. For these specialists, the defense chemistry of the host plant is usually not toxic, but they are susceptible to the toxicity of natural toxins from non-host plants (*32*). As compared to the enormous number of potential herbivores, the number of adapted monophagous species is usually very small for a particular plant species.

Quite a number of alkaloids have been tested toward herbivorous insects (Table I). In general it is observed that many alkaloids can act as feeding deterrents at higher concentrations (>1%, w/w). Given the choice, insects tend to select a diet with no or only a small dose of alkaloids. Also,

TABLE I

ACTIVITY OF ALKALOIDS AGAINST HERBIVORES (MOSTLY INSECTS AND OTHER INVERTEBRATES)

Alkaloid	Effect	ED_{50} (μg/ml, μg/g, or %)	Ref.
Alkaloids derived from tryptophan			
Acetylokaramine	Insecticidal in *Bombyx*	10	*166*
Ajmalicine	Feeding deterrent to polyphagous *Syntomis* (Lepidoptera) larvae	1%	*32*
Ajmaline	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
Brucine	Feeding deterrent to polyphagous *Syntomis* larvae	1%	*32*
	Feeding deterrent in bees (*Apis mellifera*)	0.05%	*152*
	Insecticidal for bees	0.2%	*152*
	Phagorepellent in *Pieris*, *Bombyx* (Lepidoptera)	—	*161*
Cinchonidine	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
	Feeding deterrent in bees	0.04%	*152*
	Feeding deterrent in *Agelaius* (Aves)	40 mg/kg	*175*
Cinchonine	Feeding deterrent in bees	0.007%	*152*
	Feeding deterrent in *Leptinotarsa* (Coleoptera)	—[a]	*162*
Dictamnine	Insecticidal	—	*176*
Ergocryptine	Toxic to *Oncopeltus*	—	*167*
Ergometrine	Inhibition of insect spermatophore formation	—	*164*
	Feeding deterrent to polyphagous *Syntomis* larvae	1%	*32*
Ergonovine	Toxic to *Oncopeltus*	—	*167*
Ergotamine	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
Gramine	Feeding deterrent in aphids	<1m*M*	*155,156*
	Insecticidal for *Schizaphis* (Aphidoidea)	0.01%	*157*
Harmaline	Phototoxicity in larvae of *Trichoplusia* (Lepidoptera)	4650	*66*
	Feeding deterrent to polyphagous *Syntomis* larvae	1000	*32*
Harman	Phototoxicity in larvae of *Trichoplusia*	471	*66*
	Deterrent to polyphagous larvae	—	*151*

Harmine	Photoxicity in larvae of *Trichoplusia*	5360	*66*
	Phototoxic to *Aedes* (Diptera) larvae	—	*57*
	Deterrent to polyphagous larvae	—	*151*
	Feeding deterrent to polyphagous *Syntomis* larvae	1000	*32*
	Feeding deterrent in bees	80	*152*
Hypaphorine	Feeding deterrent for seed predators	—	*163*
Kokusagine	Insecticidal	—	*176*
Maculine	Insecticidal	—	*176*
Melicopicine	Antifeedant in *Spodoptera* (Lepidoptera)	—	*97*
5-Methoxy-*N,N*-dimethyltryptamine	Antifeedant in larvae of *Anthonomus*	—	*153*
6-Methoxybenzoxazolinone	Insecticidal	—	*165*
6-Methoxydictamine	Insecticidal	—	*176*
2-Methyl-6-methoxytetrahydro-β-carboline	Antifeedant in larvae of *Anthonomus* (Coleoptera)	—	*153*
Norharman	Phototoxicity in larvae of *Trichoplusia*	380	*66*
	Toxic to *Oncopeltus*	—	*167*
Okaramines A, B	Insecticidal in *Bombyx*	0.1–3	*166*
Physostigmine	Feeding deterrent to polyphagous *Syntomis* larvae	0.01%	*32*
Quinidine	Feeding deterrent to polyphagous *Syntomis* larvae	0.01%	*32*
Quinine	Feeding deterrent in bees	0.02%	*152*
	Insecticidal for bees	0.02%	*152*
	Feeding deterrent in *Phormia* (Diptera)	0.6 m*M*	*154,160*
	Inhibition of insect spermatophore formation	—	*164*
	Feeding deterrent in *Locusta* (Orthoptera)	0.01% dry wt	*171*
	Phagorepellent in *Pieris, Bombyx, Lymantria* (Lepidoptera)	—	*161,174*
	Feeding deterrent to polyphagous *Syntomis* larvae	0.01%	*32*
	Feeding deterrent in bees	0.04%	*152*
Reserpine	Toxic for bruchids (Coleoptera)	0.1%	*159,158*
	Feeding deterrent to polyphagous *Syntomis* larvae	1%	*32*

(*continued*)

TABLE I (*Continued*)

Alkaloid	Effect	ED_{50} (μg/ml, μg/g, or %)	Ref.
Strychnine	Toxic for bruchids	0.1%	*158*
	Feeding deterrent in *Phormia*	10 m*M*	*160*
	Feeding deterrent to polyphagous *Syntomis* larvae	1%	*32*
	Feeding deterrent in bees	0.02%	*152*
	Insecticidal for bees	0.2%	*152*
	Phagorepellent in *Pieris, Bombyx, Lymantria*	—	*161*
	Feeding deterrent in *Leptinotarsa*	—	*162*
Tecleanthine	Antifeedant in *Spodoptera*	—	*97*
	Toxic for bruchids	0.1%	*158*
	Feeding deterrent in *Schistocerca* (Orthoptera)	—	*159*
	Feeding deterrent to polyphagous *Syntomis* larvae	1%	*32*
	Feeding deterrent in bees	0.2%	*152*
Vincamine	Feeding deterrent to polyphagous *Syntomis* larvae	0.01%	*32*
	Feeding deterrent in bees	0.08%	*152*
	Insecticidal for bees	0.04%	*152*
Yohimbine	Feeding deterrent in *Phormia*	2.5 m*M*	*154*
	Feeding deterrent to polyphagous *Syntomis* larvae	1%	*32*
	Feeding deterrent in bees	0.008%	*152*
Alkaloids derived from phenylalanine/tyrosine			
Aristolochic acid	Feeding deterrency, growth inhibition in larvae of *Hyphantria, Spodoptera, Lymantria*	0.25–0.5%	*168*
	Feeding deterrent in *Locusta*	0.000001% dry wt	*171*
	Toxic for *Eurytides, Papilio* (Lepidoptera)	0.5% dry wt	*168*
Berberine	Photoxicity in *Aedes* larvae	8.8 light/250 dark	*172*
	Feeding deterrency, growth inhibition in larvae of *Hyphantria, Spodoptera, Lymantria*	0.25–0.5%	*168*

	Toxic to larvae of *Euxoa* (Lepidoptera)	0.3%	*173*
	Feeding deterrent in *Phormia*	0.6 m*M*	*154*
	Toxic for *Eurytides, Parides* (Lepidoptera)	0.5% dry wt	*168*
	Feeding deterrent to polyphagous *Syntomis* larvae	1%	*32*
	Feeding deterrent in bees	0.01%	*152*
	Insecticidal for bees	0.003%	*152*
	Phagorepellent in *Pieris, Bombyx*	—	*161*
	Feeding deterrent in *Leptinotarsa*	—	*162*
Boldine	Feeding deterrent to polyphagous *Syntomis* larvae	0.01%	*32*
Canadine	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
Chelidonine	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
Cocculolidine	Feeding deterrent in *Spodoptera, Oraesia* (Lepidoptera)	—	*170*
Codeine	Feeding deterrent in *Phormia*	10 m*M*	*154*
Colchicine	Feeding deterrent in *Locusta*	0.001% dw	*171*
	Toxic for bruchids	0.1%	*158*
	Feeding deterrent to polyphagus *Syntomis* larvae	0.01%	*32*
	Feeding deterrent in bees	0.2%	*152*
	Insecticidal for bees	0.03%	*152*
	Feeding deterrent in *Agelaius*	22 mg/kg	*175*
	Insecticidal to *Leptinotarsa*	—	*162*
Emetine	Feeding deterrent to polyphagus *Syntomis* larvae	0.1%	*32*
L-Ephedrine	Toxic for bruchids	0.1%	*158*
	Feeding deterrent to polyphagus *Syntomis* larvae	0.1%	*32*
	Feeding deterrent in bees	0.09%	*152*
Glaucine	Feeding deterrency, growth inhibition in larvae of *Hyphantria, Spodoptera, Lymantria*	0.25–0.5%	*168*
Isoboldine	Feeding deterrent in *Prodenia, Oraesia*	—	*170*
Laudanosine	Feeding deterrency, growth inhibition in larvae of *Hyphantria, Spodoptera, Lymantria*	0.25–0.5%	*168*
Lycoricidine	Antifeedant in *Eurema* (Lepidoptera)	—	*169*
Lycoricidinol	Antifeedant in *Eurema*	—	*169*

(*continued*)

TABLE I (*Continued*)

Alkaloid	Effect	ED_{50} (μg/ml, μg/g, or %)	Ref.
Morphine	Phagorepellent in *Pieris*	—	*161*
	Feeding deterrent in *Leptinotarsa*	—	*162*
Noscapine	Feeding deterrent to polyphagous *Syntomis* larvae	0.01%	*32*
Papaverine	Feeding deterrency, growth inhibition in larvae of *Hyphantria, Spodoptera, Lymantria*	0.25–0.5%	*168*
	Feeding deterrent in *Phormia*	10 m*M*	*160*
	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
	Feeding deterrent in *Leptinotarsa*	—	*162*
Salsoline	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
Sanguinarine	Feeding deterrency, growth inhibition in larvae of *Hyphantria, Spodoptera, Lymantria*	0.25–0.5%	*168*
	Feeding deterrent to polyphagous *Syntomis* larvae	1%	*32*
	Feeding deterrent in *Leptinotarsa*	—	*162*
Quinolizidine alkaloids			
Anagyrine	Nematicidal in *Bursaphelenchus*	6	*216*
13-*trans*-Cinnamoyloxylupanine	Feeding deterrent in *Choristoneura fumiferana*	0.1 m*M*	*181*
Cytisine	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
	Feeding deterrent in *Acyrthosiphon pisum*	0.02%	*179*
	Feeding deterrent in *Formica rufa* (Hymenoptera)	ED_{100} 0.1%	*185*
	Nematicidal in *Bursaphelenchus*	1	*216*
	Feeding deterrent in molluscs (*Helix*)	2.5 m*M*	*219*
2,3-Dehydro-*O*-(2-pyrrolylcarbonyl)virgiline	Molluscicidal in *Biomphalaria*	—	*220*

Lupanine	Feeding deterrent to polyphagus *Syntomis* larvae	0.1%	*32*
	Reduction of growth and survivorship in *Spodoptera*	—	*180*
	Lethal to *Plutella maculipennis*	LD_{100} 6 m*M*	*183,184*
	Lethal in *Dysdercus* (Homoptera)	LD_{100} 12 m*M*	*183,184*
	Lethal in *Phaedon* (Coleoptera)	LD_{100} 12 m*M*	*183,184*
	Lethal in *Ceratitis* (Diptera)	LD_{100} 3 m*M*	*183,184*
	Feeding deterrent in *Formica rufa*	ED_{100} 1%	*185*
	Feeding deterrent in molluscs (*Helix*)	1–7 m*M*	*219*
Lupinine	Insecticidal in *Melanoplus* (Orthoptera)	—	*178*
	Feeding deterrence in *Acyrthosiphon pisum*	0.08%	*179*
Matrine	Active against *Dipylidium, Fasciola, Angiostrongylus*	—	*217,218*
N-Methylcytisine	Nematicidal in *Bursaphelenchus*	1–2	*216*
	Active against *Dipylidium, Fasciola, Angiostrongylus*	—	*217,218*
17-Oxosparteine	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
Sparteine	Feeding deterrent in *Acyrthosiphon pisum*	0.01%	*179*
	Feeding deterrent for *Entomoscelis* (Coleoptera)	1–10 m*M*	*177*
	Toxic for bruchids	0.1%	*158*
	Feeding deterrent in *Phormia*	10 m*M*	*160*
	Feeding deterrent to polyphagus *Syntomis* larvae	0.1%	*32*
	Feeding deterrent in bees	0.03%	*152*
	Insecticidal for bees	0.05%	*152*
	Phagorepellent in *Pieris*	—	*161*
	Reduction of growth and survivorship in *Spodoptera*	—	*180*
	Feeding deterrent in *Manduca sexta* (Lepidoptera)	0.05%	*182*
	Lethal to *Plutella maculipennis*	LD_{100} 50 m*M*	*183,184*
	Lethal in *Dysdercus*	LD_{100} 50 m*M*	*183,184*
	Lethal in *Ceratitis*	LD_{100} 9 m*M*	*183,184*
	Feeding deterrent in *Formica rufa*	ED_{100} 1%	*185*
	Feeding deterrent in molluscs (*Helix*)	0.7–0.8% m*M*	*219*

(*continued*)

TABLE I (*Continued*)

Alkaloid	Effect	ED_{50} (μg/ml, μg/g, or %)	Ref.
13-Tigloyloxylupanine	Feeding deterrent in *Choristoneura fumiferana*	89% at 1.4 m*M*	*181*
	Lethal to *Plutella maculipennis*	LD_{100} 12 m*M*	*183,184*
	Lethal in *Dysdercus*	LD_{100} 6 m*M*	*183,184*
	Lethal in *Phaedon*	LD_{100} 6 m*M*	*183,184*
	Lethal in *Ceratitis*	LD_{100} 6 m*M*	*183,184*
Steroidal alkaloids			
Cevadine	Insecticidal	—	*194*
Chaconine	Feeding deterrent in *Choristoneura* (Lepidoptera)	0.1 m*M*	*190*
Conessine	Molt inhibition in *Periplaneta*	—	*195*
	Phagorepellent in *Pieris, Bombyx, Lymantria, Dysdercus*	—	*161,196*
Demissidine	Feeding deterrent in *Leptinotarsa*	—	*189*
Protoveratrine B	Feeding deterrent to polyphagous *Syntomis* larvae	0.01%	*32*
Solacaudine	Feeding deterrent in *Leptinotarsa*	—	*189,191*
Soladulcine	Feeding deterrent in *Leptinotarsa*	—	*189*
Solamargine	Insecticidal in *Earias*	—	*192*
Solanidine	Feeding deterrent in *Choristoneura*	0.1 m*M*	*190*
Solanine	Feeding deterrent in *Chloristoneura*	1 m*M*	*190*
	Feeding deterrent in *Pieris*	0.4 μ*M*	*174*
	Feeding deterrent in *Leptinotarsa*	—	*189*
Solanocapsine	Feeding deterrent for *Manduca*	5 m*M*	*193*
Solasonine	Insecticidal in *Earias*	—	*192*
Tomatidine	Feeding deterrent in *Choristoneura*	1 m*M*	*190*
	Feeding deterrent to polyphagous *Syntomis* larvae	1%	*32*
	Feeding deterrent in *Leptinotarsa*	—	*189*

Tomatine	Feeding deterrent for *Locusta*	0.1%	*186*
	Growth inhibition in *Heliothis* (Lepidoptera)	0.9 m*M*	*187*
	Feeding deterrent in *Choristoneura*	0.1 m*M*	*190*
	Feeding deterrent in *Melanoplus*	—	*178*
	Deterrent in *Locusta*	0.15% dry wt	*171*
	Feeding deterrent in *Phormia*	10 m*M*	*160*
	Growth inhibition in *Hyposoter* (Hymenoptera)	20 μmol/g	*188*
	Phagorepellent in *Pieris*	—	*161*
	Phagorepellent in *Leptinotarsa*	—	*189*
Veratridine	Insecticidal	—	*194*
Veratrine	Feeding deterrent in *Schistocerca*	—	*159*
	Insecticidal to *Leptinotarsa*	—	*162*
Tropane alkaloids			
Atropine	Feeding deterrent in *Phormia*	0.6 m*M*	*154,160*
	Toxic for bruchids	0.1%	*158*
	Phagorepellent in *Pieris*	—	*161*
Cocaine	Feeding deterrent in *Leptinotarsa*	—	*162*
Hyoscyamine	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
	Feeding deterrent in bees	0.005%	*152*
	Insecticidal for bees	0.1%	*152*
Scopine	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
Scopolamine	Feeding deterrent to polyphagous *Syntomis* larvae	0.01%	*32*
	Feeding deterrent in bees	0.03%	*152*
	Phagorepellent in *Pieris, Bombyx*	—	*161*
Tropine	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
	Feeding deterrent in bees	0.2%	*152*
Polyhydroxy alkaloids			
Castanospermine	Feeding deterrent in aphids and greenbugs	0.1 m*M*	*197*
Deoxynojirimycine	Feeding deterrent in aphids and greenbugs	2.5 m*M*	*197*
6-Epicastanospermine	Feeding deterrent in aphids and greenbugs	5 m*M*	*197*

(*continued*)

TABLE I (*Continued*)

Alkaloid	Effect	ED_{50} (μg/ml, μg/g, or %)	Ref.
Pyrrolizidine alkaloids			
Crispatine	Feeding deterrent in *Choristoneura*	1.6 m*M*	*198*
N-Formylloline	Toxic to *Oncopeltus*	—	*167*
Heliotrine	Feeding deterrent in *Choristoneura*	1.6 m*M*	*198*
	Feeding deterrent in bees	0.09%	*152*
	Insecticidal for bees	0.1%	*152*
Jacobine	Feeding deterrent in *Locusta*	0.001% dry wt	*171*
Jaconine	Feeding deterrent in *Locusta*	0.05% dry wt	*171*
Lasiocarpine	Feeding deterrent in *Choristoneura*	1.2 m*M*	*198*
Perloline	Feeding deterrent in *Locusta*	0.1% dry wt	*171*
	Toxic to *Oncopeltus*	—	*167*
Senecionine	Feeding deterrent in *Choristoneura*	1.6 m*M*	*198*
	Deterrent in *Locusta*	0.001% dry wt	*171*
Senkirkine	Feeding deterrent in *Choristoneura*	1 m*M*	*198*
Miscellaneous alkaloids			
Aconitine	Feeding deterrent to polyphagous *Syntomis* larvae	1%	*32*
	Insecticidal to *Leptinotarsa*	—	*162*
2,5-Alkylpyrroline (ant)	Toxic to *Locusta, Pieris, Musca*	—	*213*
Anabasine	Insecticidal	—	*211*
	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
Anacycline	Insecticidal	—	*211*
Anonaine	Insecticidal	—	*194*
Arecoline	Feeding deterrent in *Phormia*	10 m*M*	*160*
	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*

Caffeine	Feeding deterrent in *Phormia*	2.5 m*M*	*154,160*
	Feeding deterrent in Lepidoptera, Coleoptera, Diptera	0.007–3%	*202*
	Toxic for bruchids	1%	*158*
	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
	Feeding deterrent in bees	0.03%	*152*
	Insecticidal for bees	0.2%	*152*
	Feeding deterrent in *Agelaius*	14 mg/kg	*175*
	Phagorepellent in *Bombyx, Lymantria*	—	*161*
Capsaicin	Phagorepellent in *Leptinotarsa*	—	*199*
Celastrus alkaloids	Antifeedants in *Pieris* (Lepidoptera), *Ostrina, Tribolium* (Coleoptera)	—	*203*
Cocculolidine	Insecticidal	—	*170*
Coniine	Feeding deterrent in *Phormia*	5 m*M*	*154*
	Feeding deterrent in *Agelaius*	77 mg/kg	*175*
Cycloheximide	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
Cyclopyazonic acid	Insecticidal in *Bombyx*	—	*207*
Delphinine	Insecticidal to *Leptinotarsa*	—	*162*
Demethylhomolycorine	Antifeedant in *Eurema*	—	*169*
Deoxyvasicine	Antifeedant in *Aulacophora, Dysdercus, Epilachna* (Coleoptera)	—	*209*
Dihydrowisanine	Insecticidal in *Sitophilus* (Coleoptera), feeding deterrent	—	*204*
2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine	Toxic to *Callosobruchus* (Coleoptera)	0.03%	*212*
	Feeding deterrent to locusts	—	*212*
DIMBOA/MBOA[b]	Resistance toward *Ostrinia, Sesamia* (Coleoptera), *Schizaphis, Metopolophium, Rhopalosiphon, Sitobion* (Aphidoidea)	—	*106*
Echinacein	Insecticidal	—	*211*
Halostachine	Toxic to *Oncopeltus*	—	*167*
	Insecticidal to *Leptinotarsa*	—	*162*
Isoboldine	Insecticidal, deterrent in *Spodoptera*	—	*170*
Lobeline	Feeding deterrent to polyphagous *Syntomis* larvae	1%	*32*
	Feeding deterrent in bees	0.008%	*152*

(*continued*)

TABLE I (*Continued*)

Alkaloid	Effect	ED_{50} (μg/ml, μg/g, or %)	Ref.
Methoxy-3-alkylpyrazines	Evocative, alerting odor to herbivores and predators	—	*214*
Methyllycaconitine	Insecticidal in *Spodoptera, Heliothis, Musca*	—	*200*
Muscimol	Induction of food aversion in *Opossum*	—	210
Nicotine	Antifeedant in larvae of *Anthonomus*	—	*153*
	Feeding deterrent in *Locusta*	0.02%–0.002%	*186,171*
	Insecticidal in *Culex* (Diptera), *Spodoptera*		*201*
	Toxic for bruchids	0.1%	*158*
	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
	Feeding deterrent in bees	0.03%	*152*
	Insecticidal for bees	0.2%	*152*
	Feeding deterrent in *Agelaius*	50 mg/kg	*175*
	Nematicidal in *Bursaphelenchus*	1	*216*
Nornicotine	Feeding deterrent in *Melanoplus*	—	*178*
Pellitorine	Insecticidal	—	*211*
Pergularinine	Antifeedant against *Spodoptera*	12 ppm	*208*

Pilocarpine	Feeding deterrent in *Phormia*	2.5 m*M*	*154*
	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
	Phagorepellent in *Pieris, Bombyx*	—	*161*
Pipercide	Insecticidal	—	*205*
Piperine	Insecticidal in *Sitophilus*, feeding deterrent	—	*204*
	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
Roemerine	Insecticidal	—	*194*
Ryanodine	Contact poison	—	*194*
Spilanthol	Insecticidal	—	*211*
Stemofoline	Insecticidal to *Bombyx, Mamestra* (Lepidoptera)	—	*206*
Stemonine	Insecticidal to *Bombyx, Mamestra*	—	*206*
Stemospironine	Insecticidal to *Bombyx, Mamestra*	—	*206*
Theobromine	Toxic for bruchids	1%	*158*
Tylophorinine	Antifeedant against *Spodoptera*	8.6 ppm	*208*
Tripiperideine	Feeding deterrent to polyphagous *Syntomis* larvae	0.1%	*32*
Tylophorine	Antifeedant against *Spodoptera*	2.9 ppm	*208*
Vasicine	Antifeedant in *Aulacophora, Dysdercus, Epilachna*	—	*209*
Vasicinol	Antifeedant in *Aulacophora, Dysdercus, Epilachna*	—	*209*
	Antifertility effects in *Dysdercus* and *Tribolium*	—	*209*
Vasicinone	Antifeedant in *Aulacophora, Dysdercus, Epilachna*	—	*209*
Wisanine	Insecticidal in *Sitophilus*, feeding deterrent	—	*204*
Xestoaminol A	Nematicidal in *Nippostrongylus*	—	*112*

[a] —, No ED_{50} value recorded.

[b] Hydroxamic acids (4-hydroxy-7-methoxy-1,4-benzoxazin-3-one).

specialists avoid most "toxins" except those of their host plants. These data indicate that under natural conditions plants with a high content of alkaloids should be safe from most herbivorous insects, with the exception of particular monophagous species or a few very potent polyphagous ones.

If insects have no choice or if they are very hungry, the deterrency threshold value is much reduced, and they often feed on a diet with alkaloids that they would normally avoid (*15,32*). In this case we have the chance to test the toxicity of an ingested alkaloid. If insects do not take up alkaloid-containing food, alkaloid toxicity can be assessed to some degree by topical application or by injection (Table I).

As can be seen from Table I a substantial number of alkaloids display significant insect toxicity, including nicotine, piperine, lupine alkaloids, caffeine, gramine, strychnine, berberine, ephedrine, and steroidal alkaloids. Only the specialists can tolerate the respective alkaloids. The tobacco hornworm (*Manduca sexta*), for example, can grow on a diet with more than 1% nicotine without any adverse effects. Most of the nicotine is either degraded or directly eliminated via the Malpighian tubules and in feces (*182*). Because nicotine binds to the acetylcholine (ACH) receptor, it is likely that in *Manduca* this receptor has been modified in such a way that ACH can still bind, but not nicotine (so-called target site modification).

The toxic effects of alkaloids in insects (Table I) can be caused by their interference with diverse cellular and intracellular targets. Since most mechanisms have not yet been elucidated for insects, this issue is discussed below in the section on vertebrate toxicity (see Table IV). With some caution we can extrapolate to insect toxicity.

2. *Vertebrates*

Because *Homo sapiens* and domestic animals are largely herbivores, a voluminous body of information on the adverse effects of secondary metabolites has accumulated over the centuries. Many allelochemicals and alkaloids are feeding deterrents for vertebrates, owing to their bitter or pungent taste or bad smell, and instinctively a foul-smelling, bitter, or pungent diet is normally avoided. Examples of bitter alkaloids (at least for man) are quinine, strychnine, brucine, and sparteine, and for pungent alkaloids are capsaicin, and piperine. It should be recalled that these taste properties are not identical for all animals. For example, geese, which are obligate herbivores, hardly avoid food with alkaloids or smelly compounds (amines, mercaptoethanol) that man would hardly touch (*185*). Conversely, fragrances that are attractive to us are highly repellent to geese (*185*). Even within a given population taste can differ significantly. It has been observed that a substantial proportion of *Homo sapiens* cannot detect

the smell of HCN, whereas others are highly sensitive. Furthermore, olfactory sensitivity can differ with age, sex, and hormonal cycles.

Bitterness varies with the chemical structure of an alkaloid. With the quinolizidine alkaloids (QAs) the following scale was assessed for man: Mean detection levels are 0.00085% for sparteine, 0.0021% for lupanine, and 0.017% for hydroxylupanine (*503*). Whereas we know a few parameters of olfactory qualities in *Homo sapiens*, often much less or hardly anything is known for most other vertebrates.

Alkaloids are famous for their toxic properties in vertebrates, and plants that produce alkaloids are often classified by man as poisonous or toxic plants. For a number of alkaloids the respective LD_{50} values have been determined with laboratory animals, especially mice, but also rats, guinea pigs, cats, rabbits, dogs, or pigeons. Table II presents an overview for 132 alkaloids, including the very poisonous alkaloids aconitine, coniine, atropine, brucine, curarine, ergocornine, physostigmine, strychnine, colchicine, germerine, veratridine, cytisine, delphinidine, and nicotine. Toxicity is usually highest if the alkaloids are applied parenterally [intravenously (i.v.), intraperitoneally (i.p.), and subcutaneously (s.c.)] as compared to oral application [per os (p.o.)]. Also, some of the alkaloids which are made or stored by animals are strong vertebrate poisons, including batrachotoxin, batrachotoxinin A, anabasine, glomerine, maitotoxin, nereistoxin, palytoxin, saxitoxin, and tetrodotoxin (*1,28,29,259*). Although the general toxicity of alkaloids differs from species to species, the data in Table II generally show that many alkaloids are more or less toxic to vertebrates.

3. Mode of Action of Alkaloids in Animals

The toxic effects observed with intact animals has its counterpart in the cytotoxic effect, which has been recorded for nearly 180 alkaloids (Table III). These data have been obtained by screening many natural products for anticancer activity. However, an alkaloid that can kill a cancer cell is usually also toxic for "normal" cells. Therefore, the data shown in Table III are another indication of the general toxicity of alkaloids toward animals. Because this toxicity applies also for herbivores, the production of alkaloids by plants can certainly be interpreted as a potent antiherbivore mechanism.

For a number of alkaloids the mechanisms underlying the toxic effects have already been elucidated in some detail. We can distinguish molecular targets and processes that are important for all cells, such as synthesis of DNA, RNA, and proteins, replication, transcription, translation, membrane assembly and stability, electron chains, or metabolically important enzymes or proteins including receptors, hormones, and signal compounds (Table IV). In the following we discuss some of these toxic effects.

TABLE II

TOXICITY OF ALKALOIDS IN VERTEBRATES

Alkaloid	Test System	LD	Ref.
Alkaloids derived from tryptophan			
Annomontine	Mouse	LD_{50} p.o. >1000 mg/kg	*257*
Aspidospermine	Mouse	LD_{50} i.p. 40 mg/kg	*149*
Brucine	Rat	LD_{50} p.o. 1 mg/kg	*149*
Cinchonidine	Rat	LD_{50} i.p. 206 mg/kg	*149*
	Agelaius	LD_{50} p.o. 100 mg/kg	*175*
Cinchonine	Rat	LD_{50} i.p. 152 mg/kg	*149*
Curarine	—	LD_{100} i.p. 0.34 mg/kg	*258*
Ellipticine	Mouse	LD_{50} i.v. 19–22 mg/kg, p.o. 178–204 mg/kg	*149*
Ergocornine	Rabbit	LD_{50} i.v. 1.2 mg/kg	*149*
Ergocryptine	Rabbit	LD_{50} i.v. 1.1 mg/kg	*149*
Ergometrine	Mouse	LD_{50} i.v. 0.15 mg/kg	*259*
Ergotamine	Mouse	LD_{50} i.v. 62 mg/kg	*149*
	Rat	LD_{50} i.v. 80 mg/kg	*149*
	Rabbit	LD_{50} i.v. 3.5 mg/kg	*259*
Harman	Mouse	LD_{50} i.p. 50 mg/kg	*149*
Harmine	Mouse	LD_{50} i.v. 38 mg/kg	*149*
Methoxyannomontine	Mouse	LD_{50} i.p. 30–100 mg/kg, p.o. >1000 mg/kg	*257*
Physostigmine	Mouse	LD_{50} p.o. 4.5 mg/kg	*149*
Psilocybin	Mouse	LD_{50} i.v. 285 mg/kg	*149*
	Rat	LD_{50} i.v. 280 mg/kg	*149*
	Rabbit	LD_{50} i.v. 12.5 mg/kg	*149*
Quinidine	Rat	LD_{50} i.v. 30 mg/kg, p.o. 263 mg/kg	*149*
Quinine	*Agelaius*	LD_{50} p.o. 100 mg/kg	*175*
Reserpine	*Agelaius*	LD_{50} p.o. 100 mg/kg	*175*
Roquefortine A	Mouse	LD_{50} i.p. 340 mg/kg	*259*
Roquefortine C	Mouse	LD_{50} i.p. 169–184 mg/kg	*259*

Strychnine	*Agelaius*	LD_{50} p.o. 6 mg/kg	*175*
	Starling	LD_{50} p.o. 6 mg/kg	*175*
	Rat	LD_{50} i.v. 0.9 mg/kg	*149*
	Dog	LD_{100} p.o. 0.3–1.2 mg/kg, s.c. 0.003–0.02 mg/kg	*259*
Toxiferine	—	LD_{100} i.p. 0.03 mg/kg	*258*
Vinblastine	Mouse	LD_{50} i.v. 9.5 mg/kg	*149*
Vincamine	Mouse	LD_{50} i.v. 75 mg/kg, p.o. 1000 mg/kg	*149*
Vincristine	Mouse	LD_{50} i.p. 5.2 mg/kg	*149*
Alkaloids derived from phenylalanine and tyrosine			
Aristolochic acid	Mouse	LD_{50} i.v. 38(m)–70(f) mg/kg, p.o. 56(m)–106(f) mg/kg	*149*
Berberine	Mouse	LD_{50} i.p. 23 mg/kg	*149*
Bulbocapnine	Mouse	LD_{50} p.o. 413 mg/kg	*259*
Canadine	Mouse	LD_{50} p.o. 940 mg/kg, s.c. 790 mg/kg, i.v. 100 mg/kg	*149*
Chelerythrine	Mouse	LD_{100} s.c. 95 mg/kg	*259*
Chelidonine	Mouse	LD_{50} i.v. 35 mg/kg	*149*
Codeine	Mouse	LD_{50} s.c. 300 mg/kg	*149*
Colchiceine	Mouse	LD_{50} i.p. 84 mg/kg	*149*
Colchicine	Mouse	LD_{50} i.v. 4.1 mg/kg	*149*
	Rat	LD_{50} i.v. 1.6 mg/kg	*149*
	Man	LD_{100} p.o. 0.1–0.3 mg/kg	*259*
	Agelaius	LD_{50} p.o. 32 mg/kg	*175*
	Starling	LD_{50} p.o. 21 mg/kg	*175*
Corydaline	Mouse	LD_{50} i.v. 135 mg/kg	*149*
Emetine	Rat	LD_{50} i.v. 12.1 mg/kg	*149*
	Mouse	LD_{50} s.c. 32 mg/kg	*149*
Galanthamine	Mouse	LD_{50} i.v. 8 mg/kg, p.o. 18.7 mg/kg, s.c. 11.1 mg/kg	*149*
Glaucine	Mouse	LD_{50} i.v. 98 mg/kg, p.o. 401 mg/kg	*149*

(*continued*)

TABLE II (*Continued*)

Alkaloid	Test System	LD	Ref.
Isothebaine	Mouse	LD_{50} i.p. 26 mg/kg	*260*
Mescaline	*Agelaius*	LD_{50} p.o. 100 mg/kg	*175*
Morphine	Mouse	LD_{50} i.v. 226–318 mg/kg	*149*
Nuciferine	Rat/mouse	LD_{50} p.o. 240–280 mg/kg	*260*
Papaverine	Mouse	LD_{50} i.v. 27.5 mg/kg, s.c. 150 mg/kg	*149*
	Rat	LD_{50} i.v. 20 mg/kg, s.c. 370 mg/kg	*149*
Protopine	Mouse	LD_{100} 100 mg/kg	*259*
	Mouse	LD_{50} i.p. 36–102 mg/kg	*260*
Sanguinarine	Rat	LD_{50} i.v. 29 mg/kg, p.o. 1658 mg/kg	*149*
	Mouse	LD_{50} s.c. 102 mg/kg, i.v. 16 mg/kg	*149*
Tazettine	Mouse	LD_{50} i.v. 100 mg/kg, i.p. 420 mg/kg	*259*
Tetrahydropalmatine	Mouse	LD_{50} i.p. 111 mg/kg	*260*
Thebaine	Mouse	LD_{50} i.p. 20 mg/kg	*259*
	Frog	LD_{50} i.p. 50 mg/kg	*260*
	Rabbit	LD_{50} i.p. 3–4 mg/kg	*260*
	Rabbit	LD_{50} s.c. 14 mg/kg	*149*
Tubocurarine	Mouse	LD_{50} p.o. 33.2 mg/kg	*149*
	Rat	LD_{50} p.o. 27.8 mg/kg	*149*
Steroidal alkaloids			
Batrachotoxin (frog)	Mouse	LD_{50} s.c. 2 μg/kg	*149*
	Man	Lethal dose 200 μg	*259*
Batrachotoxinin A	Mouse	LD_{50} s.c. 1 mg/kg	*149*
Chaconine	Rat	LD_{50} i.p. 84 mg/kg	*259*
Germerine	Rat	LD_{50} s.c. 3.7 mg/kg	*259*
Jervine	Mouse	LD_{50} i.v. 9.3 mg/kg	*149*
Protoveratrine	Rabbit	Lethal dose 0.1 mg/kg	*259*
Rubijervine	Rat	LD_{50} i.v. 70 mg/kg	*149*

Samandarine	Frog	LD_{100} 19 mg/kg	*263*
	Mouse	LD_{100} 3.4 mg/kg	*263*
	Rabbit	LD_{100} 1 mg/kg	*263*
Solanine	Hens' eggs	LD_{100} 0.3–1.5 mg/egg	*261*
	Monkey	LD_{100} i.p. 40	*262*
	Rat	LD_{50} i.p. 67 mg/kg, p.o. 590 mg/kg	*262*
	Mouse	LD_{50} i.p. 42 mg/kg	*259*
	Rabbit	Lethal dose 20–30 mg/kg i.p.	*259*
Tomatidine	*Agelaius*	LD_{50} p.o. 100 mg/kg	*175*
Tomatine	Rat	LD_{50} p.o. 900–1000 mg/kg	*149*
Veratridine	Mouse	LD_{50} i.p. 1.4 mg/kg	*149*
Tropane alkaloids			
Apoatropine	Mouse	LD_{50} p.o. 160 mg/kg, i.p. 14.1 mg/kg	*149*
Atropine	Rat	LD_{50} p.o. 750 mg/kg	*149*
	Man	Paralytic dose >10 mg	*259*
Cocaine	Rat	LD_{50} i.v. 17.5 mg/kg	*149*
	Man	Lethal dose >30 mg i.v.	*259*
Pyrrolizidine alkaloids			
7-Angeloylheliotridine	Rat	LD_{50} i.p. 260 mg/kg	*259*
Echimidine	Rat	LD_{50} i.p. 200 mg/kg	*259*
Echinatine	Rat	LD_{50} i.p. 350 mg/kg	*259*
Europine	Rat	LD_{50} p.o. 1000 mg/kg	*264*
Heliotrine	Rat	LD_{50} i.p. 300 mg/kg	*259*
Heliotrine *N*-oxide	Rat	LD_{50} i.p. 2500(f)–5000(m) mg/kg	*259*
Jacobine	Rat	LD_{50} i.p. 138 mg/kg	*259*
Lasiocarpine	Rat	LD_{50} i.p. 260 mg/kg	*259*
Monocrotaline	Rat	LD_{50} i.p. 175 mg/kg, p.o. 71 mg/kg	*149,259,265*
Retronecine	Mouse	LD_{50} i.v. 634 mg/kg	*149*
Retrosine	Rat	LD_{50} i.p. 30–150 mg/kg	*265*
Retrorsine *N*-oxide	Rat	LD_{50} p.o. 250 mg/kg, i.p. 48 mg/kg	*265*

(*continued*)

TABLE II (*Continued*)

Alkaloid	Test System	LD	Ref.
Senecionine	Rat	LD_{50} 50 mg/kg, i.p. 85 mg/kg	*259*
	Mouse	LD_{50} i.v. 64 mg/kg	*149*
Seneciphylline	Rat	LD_{50} i.p. 77 mg/kg	*259*
Supinine	Rat	LD_{50} i.p. 450 mg/kg	*259*
Quinolizidine alkaloids			
Cytisine	Cat	LD_{100} s.c. 3 mg/kg	*278*
	Dog	LD_{100} s.c. 4 mg/kg	*278*
	Goat	LD_{100} s.c. 109 mg/kg	*278*
	Mouse	LD_{50} i.v. 1.7 mg/kg, i.p. 9.3 mg/kg, p.o. 101 mg/kg	*149*
Epilupinine	Rat	LD_{50} i.p. 200–400 mg/kg	*275*
13-Hydroxylupanine	Guinea pig	LD_{100} i.p. 228 mg/kg, s.c. 456 mg/kg	*268*
	Rat	LD_{50} i.p. 199 mg/kg	*275*
	Mouse	LD_{50} i.p. 172 mg/kg	*276*
Lupinine	Guinea pig	LD_{100} i.p. 28–30 mg/kg	*268*
Lupanine	Guinea pig	LD_{100} i.p. 22–25 mg/kg	*268*
	Mouse	LD_{50} i.p. 80 mg/kg	*273*
	Rat	LD_{50} i.p. 180–192 mg/kg	*273*
	Guinea pig	LD_{50} i.p. 210 mg/kg	*273*
	Mouse	LD_{50} i.p. 175 mg/kg, p.o. 410 mg/kg	*274*
Matrine	Mouse	LD_{50} i.p. 150 mg/kg	*311*
Matrine *N*-oxide	Mouse	LD_{50} i.p. 750 mg/kg, i.v. 150 mg/kg	*311*
N-Methylycytisine	Mouse	LD_{50} i.v. 21 mg/kg, i.p. 51 mg/kg	*149*
Nupharidine	Mouse	LD_{50} i.v. 29 mg/kg	*259*
	Rat	LD_{50} i.p. 177 mg/kg, p.o. 1464 mg/kg	*275*
17-Oxolupanine	Mouse	LD_{50} i.p. 690 mg/kg	*277*

Sparteine	Guinea pig	LD_{100} i.p. 23–30 mg/kg	*268*
	Rat	LD_{50} i.p. 42–44 mg/kg, s.c. 68–75 mg/kg	*269*
	Mouse	LD_{50} i.p. 55(m)–67(f) mg/kg, i.v. 17(m)–20(f) mg/kg, p.o. 350(m)–510(f) mg/kg	*270*
	Rabbit	LD_{100} p.o. 450 mg/kg	*271*
	Rabbit	Lethal dose i.v. 20–30 mg/kg	*272*
	Dog	Lethal dose i.v. 50–70 mg/kg	*272*
	Pigeon	Lethal dose i.v. 40–50 mg/kg	*272*
Miscellaneous alkaloids			
Aconitine	Mouse	LD_{50} i.v. 0.166 mg/kg, i.p. 0.328 mg/kg, p.o. ~1 mg/kg	*149*
	Rat	LD_{50} i.v. 0.08–0.14 mg/kg	*259*
	Cat	LD_{50} i.v. 0.07–0.13 mg/kg	*259*
	Man	Lethal dose p.o. 1.5–5 mg	*259*
Actinobolin	Mouse	LD_{50} i.v. 800 mg/kg	*149*
	Rat	LD_{50} i.v. 1550 mg/kg	*149*
Adenine	Rat	LD_{50} p.o. 745 mg/kg	*149*
α-Amanitin	Mouse	LD_{50} i.p. 0.1 mg/kg	*149*
β-Amanitin	Mouse	LD_{50} i.p. 0.4 mg/kg	*149*
Anabaseine	Mouse	LD_{50} i.v. 84 μg/kg	*230*
Antimycin A	Mouse	LD_{50} i.p. 1.8 mg/kg, s.c. 1.6 mg/kg	*149*
Arecoline	Mouse	LD_{50} s.c. 100 mg/kg	*149*
	Dog	LD_{50} s.c. 5 mg/kg	*149*
Benzoylaconitine	Rat	LD_{50} i.v. 27 mg/kg	*259*
2,3′-Bipyridyl	Mouse	LD_{50} i.v. 3500 μg/kg	*230*
Caffeine	*Agelaius*	LD_{50} i.p. 316 mg/kg	*149*
	Mouse	LD_{50} p.o. 127(m)–137(f) mg/kg	*149*
	Hamster	LD_{50} p.o. 230(m)–249(f) mg/kg	*149*
	Rabbit	LD_{50} p.o. 246(m)–224(f) mg/kg	*149*
	Rat	LD_{50} p.o. 200 mg/kg	*259*
Calcimycin	Mouse	LD_{50} i.p. 10 mg/kg	*149*

(*continued*)

TABLE II (*Continued*)

Alkaloid	Test System	LD	Ref.
Carubicin	Mouse	LD_{50} p.o. 7.3 mg/kg, i.v. 1.3 mg/kg	*149*
Carzinophilin	Mouse	LD_{50} i.v. 150 μg/kg	*149*
Coniine	*Agelaius*	LD_{50} p.o. 56 mg/kg	*175*
	Guinea pig	LD_{100} p.o. 150 mg/kg, s.c. 40 mg/kg	*259*
Cycloheximide	Mouse	LD_{50} i.v. 150 mg/kg	*149*
Damascenine	Mouse	LD_{50} p.o. 1800 mg/kg	*149*
Daunorubicin	Mouse	LD_{50} i.v. 26 mg/kg	*149*
Delphinine	Frog	LD_{50} i.p. 0.05–0.1 mg/kg	*267*
	Rabbit	LD_{50} i.p. 1.5–3.0 mg/kg	*267*
Epinephrine (adrenaline)	Mouse	LD_{50} i.p. 4 mg/kg	*149*
Glomerine	Mouse	LD_{50} p.o. 17–34 mg/kg	*259*
Hypaconitine	Mouse	LD_{50} s.c. 1.2 mg/kg	*259*
Lappaconitine	Mouse	LD_{50} i.v. 6.9 mg/kg, p.o. 20 mg/kg	*149*
Lycoctonine	Mouse	LD_{50} i.p. 350 mg/kg	*267*
Maitotoxin (algae/fish)	Mouse	LD_{100} i.p. 0.17 μg/kg	*259*
Maytansine	Rat	LD_{50} s.c. 0.48 mg/kg	*149*
Mesaconitine	Mouse	LD_{50} s.c. 0.2 mg/kg	*259*

Methyl-lycaconitine	Frog	LD_{50} i.p. 3.0–3.5 mg/kg	*267*
	Mouse	LD_{50} i.p. 18 mg/kg	*267*
Mitomycin	Mouse	LD_{50} i.v. 5–10 mg/kg	*149*
Muscimol	Rat	LD_{50} p.o. 45 mg/kg	*266*
Nemertilline	Mouse	LD_{50} i.v. 500 μg/kg	*230*
Nereistoxin	Mouse	LD_{100} s.c. 38 μg/kg	*221*
Nicotine	*Agelaius*	LD_{50} p.o. 17.8 mg/kg	*175*
	Starling	LD_{50} p.o. 42 mg/kg	*175*
	Mouse	LD_{50} i.v. 0.3 mg/kg, i.p. 9.5 mg/kg, p.o. 230 mg/kg	*149*
Nornicotine	Rat	LD_{50} i.p. 23.5 mg/kg	*149*
	Rabbit	LD_{50} i.v. 3 mg/kg	*149*
Ochratoxin	Rat	LD_{50} p.o. 20–22 mg/kg	*149*
Palytoxin	Mouse	LD_{50} i.v. 0.45 μg/kg, i.p. 0.05–0.15 μg/kg	*149*
Pellertierine	Rabbit	LD_{50} i.v. 40 mg/kg	*149*
Ricinine	*Agelaius*	LD_{50} p.o. 42 mg/kg	*259*
Saxitoxin	Mouse	LD_{50} i.p. 10 μg/kg, i.v. 3.4 mg/kg, p.o. 263 mg/kg	*149*
	Guinea pig	LD_{50} p.o. 135 μg/kg	*259*
Tetrodotoxin	Mouse	LD_{50} i.p. 10 μg/kg, s.c. 8 μg/kg, p.o. 0.3 mg/kg	*149,259*
Theobromine	Rat	LD_{50} p.o. 950 mg/kg	*259*

TABLE III
CYTOTOXIC ACTIVITY OF ALKALOIDS

Alkaloid	Effect	ED_{50}	Ref.
Alkaloids derived from tryptophan			
Annomontine	Antiamebic	50 μg/ml	*257*
Apparicine	Cytotoxic to P388 cells	—	*283*
Bisnordihydrotoxiferine	Inhibition of sarcoma 180	18 mg/kg	*284*
Boldine	Inhibition of human epidermoid carcinoma of larynx	—	*285*
Brevicolline	Photogenotoxic in CHO cells	—	*57*
Camptothecine	Antitumor properties, L1210 Walker sarcoma	—	*286*
	Cytotoxic to KB and P388 cells	0.17–0.53 μg/ml	*283*
Canthin-6-one	Photogenotoxic in CHO cells	—	*57*
Cinchonidine	Growth inhibition of *Plasmodium falciparum*	200 ng/ml	*287*
Cinchonine	Growth inhibition of *Plasmodium falciparum*	27–130 ng/ml	*287*
Conoduramine	Inhibition of P388 leukemia cells	20 μg/ml	*281*
Conodurine	Inhibition of P388 leukemia cells	26 μg/ml	*281*
Coronoaridine	Cytotoxic to P388 cells	0.43μg/ml	*283*
Ellipticine	Antitumor agent in L1210 cells	—	*288*
16-Epi-(*Z*)-isositsirikine	Antineoplastic to KB and P388 cells	1.2 μg/ml	*280*
9-Epivoacarine	Cytotoxic to P388 cells	1.7 μg/ml	*281*
Gabunamine	Inhibition of P388 leukemia cells	1.3 μg/ml	*281*
Gabunine	Inhibition of P388 leukemia cells	3.2 μg/ml	*281*
Harmaline	Growth inhibition of *Trypanosoma cruzi*	—	*289*
Harman	Photogenotoxic to CHO cells	—	*57*
	Growth inhibition of *Trypanosoma cruzi*	—	*289*
Harmine	Growth inhibition of *Trypanosoma cruzi*	—	*289*
Harmol	Growth inhibition of *Trypanosoma cruzi*	—	*289*
20-Hydroxyvoacamidine	Antineoplastic	—	*282*
Isovoacangine	Inhibition of P388 leukemia cells	18 μg/ml	*281*
Leurosidine	Antitumor activity	—	*282*
Methoxyannomontine	Antiamebic	—	*257*

9-Methoxycamptothecine	Antitumor activity in L1210, P388	0.036μg/ml	*283*
1-Methoxycanthin-6-one	Inhibition of Eagle carcinoma of nasopharynx	—	*279*
9-Methoxyellipticine	Cytotoxic	—	*282*
Olivacine	Growth inhibition of *Trypanosoma cruzi* and *Crithidia*	—	*290*
	Tumor inhibition in L1210 cells	—	*291*
	Cytotoxic to KB cells	0.4 μg/ml	*292*
Pericyclivine	Inhibition of P388 leukemia cells	13 μg/ml	*281*
Perivine	Inhibition of P388 leukemia cells	20 μg/ml	*281*
Ptelefolonium	Inhibition of animal/human cells	10 μ*M*	*256*
Quinidine	Growth inhibition of *Plasmodium falciparum*	22–80 ng/ml	*287*
Quinine	Growth inhibition of *Plasmodium berghei*	50 mg/kg	*293*
	Growth inhibition of *Trypanosoma cruzi*	—	*289*
	Growth inhibition of *Plasmodium falciparum*	45–280 ng/ml	*287*
Reserpine	Cytotoxic to Walker 256 carcinosarcoma	—	*282*
Tabernamine	Inhibition of P388 leukemia cells	2.1 μg/ml	*281*
Tubotaiwine N^4-oxide	Cytotoxic to P388 cells	1.8 μg/ml	*281*
Tubulosine	Inhibition of leukemia and carcinoma cells	0.01–0.00001 μg/ml	*174*
	Amebicidal	—	*304*
Vallesiachotamine	Cytotoxic to KB and P388 cells	1.1–3.5 μg/ml	*280*
Vinblastine	Growth inhibition of *Trypanosoma cruzi*	—	*289*
	Antitumor activity in Hodgkin's disease, testicular cancer	—	*286*
Vincristine	Antitumor activity in childhood leukemia, Wilm's tumour, lymphomas	—	*286*
Vinleurosine	Antitumor activity	—	*282*
Vinrosidine	Antitumor activity	—	*282*
Voacamine	Cytotoxic to P388 cells	2.6 μg/ml	*281*
Alkaloids derived from phenylalanine/tyrosine			
Antioquine	Growth inhibition of *Leishmania*	—	*294*
Aristolochic acid	Antitumor activity	—	*282*
Armepavine *N*-oxide	Cytotoxic to KB cells	—	*295*

(*continued*)

TABLE III (*Continued*)

Alkaloid	Effect	ED_{50}	Ref.
Berbamine	Growth inhibition of *Leishmania*	—	*294*
Berberine	Growth inhibition of *Trypanosoma cruzi*	—	*289*
	Inhibition of *Plasmodium falciparum*	—	*296*
	Cytotoxic properties	—	*282*
Berberrubine	Antitumoral	—	*297*
Capnoidine	Growth inhibition of *Trypanosoma brucei*	>200 mg/kg	*293*
Chelerythrine	Antitumor activity	—	*298*
Chelidonine	Cytotoxic	—	*282*
Chondrodendrine	Growth inhibition of *Leishmania*	—	*299*
Cissamparein	Active against nasopharyngal carcinoma	—	*282*
Claviculine	Growth inhibition of *Plasmodium berghei*	1–5 mg/kg	*293*
Cocsuline	Growth inhibition of *Leishmania*	—	*299*
Colchicine	Cytotoxic activities	—	*282*
Coptisine	Cytotoxic activity	—	*297*
Coralyne	Antileukemic to L1210, P388 cells	—	*300*
	Antitumor	—	*297*
Corpaine	Growth inhibition of *Trypanosoma brucei*	>200 mg/kg	*301*
Corydine	Cytotoxic activity	—	*282*
Curin	Active against nasopharyngal carcinoma	—	*282*
Cycleacurine	Cancerostatic	—	*282*
Cycleadrine	Cancerostatic	—	*282*
Cycleanine	Growth inhibition of *Leishmania*	—	*299*
Cycleanorine	Cancerostatic	—	*282*
Cycleapeltine	Cancerostatic	—	*282*
Daphnandrine	Growth inhibition of *Leishmania*	—	*299*
	Growth inhibition of *Trypanosoma cruzi*	—	*299*
Dehydroemetine	Low anticancer activity	—	*302*
Demecolcine	Cytotoxic activity	—	*282*
Dicentrine *N*-oxide	Cytotoxic to KB cells	—	*295*

Emetine	Growth inhibition of *Trypanosoma cruzi*	—	*289*
	Weak anticancer activity	—	*303*
Fagaronine	Cytotoxic to KB cells, leukemia L1210, P388 cells	—	*88,286*
Fangchinoline	Active against nasopharyngal carcinoma	—	*282*
Glaziovine	Cytotoxic	—	*282*
Gyrocarpine	Growth inhibition of *Leishmania*	—	*299*
	Growth inhibition of *Trypanosoma cruzi*	—	*294*
Isochondrodendrine	Active against nasopharyngal carcinoma	—	*282*
Isocorypalmine	Antitumoral	—	*297*
Jatrorrhizine	Inhibition of *Plasmodium falciparum*	—	*296*
Krukovine	Growth inhibition of *Leishmania*	—	*299*
Limacine	Growth inhibition of *Leishmania*	—	*299*
Liriodenine	Active against nasopharyngal tumors	—	*282*
	Cytotoxic to A-549, HCT-8, KB, P388 cells	—	*295*
Lycorine	Toxic to Rauscher virus NIH/3T3 cells	0.2 μg/ml	*147*
O-Methylatheroline	Cytotoxic	—	*282*
Nitidine	Antileukemic to mouse, L1210, P388 cells	—	*300*
	Antitrypanosomal		
Obaberine	Growth inhibition of *Leishmania*	—	*299*
	Growth inhibition of *Trypanosoma cruzi*	—	*294*
Oxodicentrine	Cytotoxic to A-549, HCT-8, P388 cells	—	*295*
Oxoglaucine	Cytotoxic to HCT-8, KB cells	—	*295*
Oxo-*O*-methylbulbocapnine	Cytotoxic to A-549, HCT-8 cells	—	*295*
Oxopurpureine	Cytotoxic	—	*282*
Oxoxylopine	Cytotoxic to A-549, HCT-8, KB, P388 cells	—	*295*
Palmatine	Antitumoral	—	*297*
	Inhibition of *Plasmodium falciparum*	—	*296*
Penduline	Cytostatic	—	*282*
Pheantine	Growth inhibition of *Leishmania*	—	*299*
Protopine	Cytotoxic	—	*282*
Pseudolycorine	Toxic to Rauscher virus NIH/3T3 cells	1.0 μg/ml	*147*

(*continued*)

TABLE III (*Continued*)

Alkaloid	Effect	ED_{50}	Ref.
Sanguinarine	Antitumor activity	—	*298*
Tetrandrine	Active against Walker carcinoma cells	—	*286,305*
Thalfoeditine	Active against carcinoma 256 in rats	—	*282*
Thalicarpine (=thaliblastine)	Antileukemic to Walker S, TLX-5 cells	—	*306*
Thalidasine	Active against carcinosarcoma 256 in rats	—	*282*
Xylopine	Cytotoxic to A-549, HCT-8, KB, P388 cells	—	*295*
Acridone alkaloids			
Acronycine	Active against mouse leukemia L1210 cells	—	*145*
	Growth inhibition of *Plasmodium yoelii*	10 μg/ml	*307*
Atalaphillidine	Active against mouse leukemia L1210 cells	—	*145*
	Growth inhibition of *Plasmodium yoelii*	10μg/ml	*307*
Atalaphillinine	Active against mouse leukemia L1210 cells	—	*145*
	Growth inhibition of *Plasmodium yoelii*	10 μg/ml	*307*
Citpressine I	Active against mouse leukemia L1210 cells	—	*145*
Citracidone I	Active against mouse leukemia L1210 cells	—	*145*
Citrusinine I	Active against mouse leukemia L1210 cells	—	*145*
Dercitine (sponge)	Active against P388, HCT-8 cells	—	*144*
Des-*N*-methylnoracronycine	Growth inhibition of *Plasmodium yoelii*	10 μg/ml	*307*
Dimethoxyacronycine	Active against some leukemia L1210 cells	—	*145*
Glandisine	Growth inhibition of *Plasmodium yoelii*	10 μg/ml	*307*
Glycobismine A	Growth inhibition of *Plasmodium yoelii*	10 μg/ml	*307*
Glycocitrine I	Active against mouse leukemia L1210 cells	—	*145*
	Growth inhibition of *Plasmodium yoelli*	10 μg/ml	*307*
Glyfoline	Active against mouse leukemia L1210 cells	—	*145*
Grandisine	Active against mouse leukemia L1210 cells	—	*145*
5-Hydroxy-*N*-methylseverifoline	Growth inhibition of *Plasmodium yoelii*	10 μg/ml	*307*
	Active against mouse leukemia L1210 cells	—	*145*
5-Hydroxynoracronycine	Active against mouse leukemia L1210 cells	—	*145*
	Growth inhibition of *Plasmodium yoelii*	10 μg/ml	*307*

Melicopine	Antitumor activity	—	*282*
5-Methoxyacronycine	Active against mouse leukemia L1210 cells	—	*145*
	Growth inhibition of *Plasmodium yoelii*	10 μg/ml	*145*
N-Methylatalaphilline	Active against mouse leukemia L1210 cells	—	*145*
	Growth inhibition of *Plasmodium yoelii*	10 μg/ml	*307*
1,3-*O*-Methyl-*N*-methylacridone	Growth inhibition of *Plasmodium yoelii*	10 μg/ml	*307*
Normelicopidine	Antitumor activity	—	*282*
Steroidal alkaloids			
Solamargine	Cytotoxic to PLC, PRF cells	—	*310*
β-Solamarine	Antitumor activity	—	*282*
Solasodine	Cytotoxic to PLC, PRF cells	—	*310*
Solasonine/solamargine	Inhibition of skin cancer	—	*309*
Pyrrolizidine alkaloids			
Echinatine-*N*-oxide	Active against P388 mouse leukemia	—	*311*
Europine *N*-oxide	Active against P388 mouse leukemia	—	*311*
Fulvine	Antitumor activity	—	*282*
Heliotrine	Antitumor activity	—	*282*
Heliotrine *N*-oxide	Antitumor activity	—	*282*
Indicine *N*-oxide	Active against P388 mouse leukemia	—	*311*
Lasiocarpine	Antitumor activity	—	*282*
Monocrotaline	Antileukemic effects	—	*286*
Senecionine	Antitumor activity	—	*282*
Senecionine *N*-oxide	Antitumor activity	—	*282*
Spectabiline	Antitumor activity	—	*282*
Supinine	Antitumor activity	—	*282*
Quinolizidine alkaloids			
Matrine	Antitumor activity in Ehrlich ascites tumor	—	*311*
	Antitumor activity in mouse sarcoma 180	—	*311*
Oxymatrine	Antitumor activity in mouse sarcoma 180	—	*311*
Miscellaneous alkaloids			
Arecoline	Growth inhibition of *Trypanosoma cruzi*	—	*289*
	Inhibition of intestinal cestodes and nematodes	—	*312*

(*continued*)

TABLE III (*Continued*)

Alkaloid	Effect	ED_{50}	Ref.
Aristolactam	Antitumoral in lung cells, colon tumors	—	*313*
Atropine	Growth inhibition of *Trypanosoma cruzi*	—	*289*
Cephalomannine	Antileukemic agent	—	*314*
	Active against KB cells	0.38 μg/ml	*315*
Crinamine	Toxic to Rauscher virus NIH/3T3 cells	0.2 μg/ml	*147*
Cryptopleurine	Active against KB carcinoma cells	—	*133*
Demethyltylophorinine	Antitumor activity	—	*282*
Deoxyharringtonine	Active against lymphocytic leukemia	—	*316,317*
Didemnins	Antitumor activity in L1210 cells	0.01–0.005 μg/ml	*109*
trans-Dihydronarciclasine	Active against P388 mouse leukemia	0.003 μg/ml	*323*
Diplamine	Cytotoxic toward L1210 leukemia cells	0.002 μg/ml	*189*
Ecteinascidins (tunicate)	Active in P388 mouse leukemia, L1210 cells	0.0001–0.08 μg/ml	*109*
Emarginatine B	Cytotoxic in KB cells	0.4 μg/ml	*318*
Febrifugine	Antitumor activity	—	*282*
Haemanthamine	Toxic to Rauscher virus NIH/3T3 cells	0.2 μg/ml	*147*
Harringtonine	Active against lymphocytic leukemia	—	*316,317*

Homoharringtonine	Active against lymphocytic leukemia	—	*316,317*
6-Hydroxycrinamine	Toxic to Rauscher virus NIH/3T3 cells	0.2 μg/ml	*147*
Isoharringtonine	Active against lymphocytic leukemia	—	*316,317*
Jatropham	Active in P388 mouse leukemia	—	*282*
Maytansine	Antileukemic agent	—	*319*
Narciclasine	Toxic to Rauscher virus NIH/3T3 cells	0.005 μg/ml	*147*
Odorinol	Antileukemic agent	—	*320*
Pancratistatin	Antineoplastic	—	*321*
Patellamid A (tunicate)	Antileukemic agent	2–4 μg/ml	*320*
Pilocarpine	Antitumor activity	—	*282*
Precriwelline	Toxic to Rauscher virus NIH/3T3 cells	0.05 μg/ml	*147*
Pretazettine	Antileukemic agent	—	*322*
	Toxic to Rauscher virus NIH/3T3 cells	0.05 μg/ml	*147*
Sesbanimide	Antileukemic agent	—	*320*
Solapalmitenine	Antitumor activity	—	*282*
Solapalmitine	Antitumor activity	—	*282*
Tylocrepine	Antitumor activity	—	*282*
Tylophorine	Antitumor activity	—	*282*
Ungeremine	Cytotoxic to S180 tumor cells	—	*114*

TABLE IV

MOLECULAR TARGETS OF ALKALOIDS: PROTEINS, NUCLEIC ACIDS, BIOMEMBRANES, AND ELECTRON CHAINS

Alkaloid	Effect	Ref.
Indole and quinoline alkaloids		
Acronycine	Inhibition of nucleoside transport	*360*
Anonaine	Inhibition of adenylate cyclase	*361*
Boldine	Quenching of singlet oxygen	*362*
Brucine	Quenching of singlet oxygen	*362*
	Inhibition of muscle lactate dehydrogenase	*363*
	Binding to glycine receptor	*364*
Camptothecine	Inhibition of 45 S rRNA transcription	*365,366*
β-Carboline-1-propionic acid	Inhibition of cAMP phosphodiesterase	*357*
Dictamnine	Monofunctional photoaddition to DNA	*367*
Ellipticine	Intercalation with DNA	*368*
	Inhibition of mitochondrial respiration	*369*
	Inhibition of cytochrome *c* oxidase, interaction with phospholipids	*358*
Ergot alkaloids	Interaction with dopamine, serotonin, and norepinephrine receptors	*370,371*
Ervatamine	Inhibition of Na^+ channels	*372*
Eseridine	Cholinergic	*149*
Eserine (physostigmine)	Inhibition of acetylcholinesterase	*259,373*
1-Ethyl-β-carboline	Inhibition of cAMP phosphodiesterase	*357*
Gelsemine	Modulation of glycine neurochemical activity	*364*
Gramine	Uncoupling of photophosphorylation	*374*
Harmaline	Inhibition of Na^+,K^+-ATPase, Na^+ transport, and monoamine oxidase A	*375,376*
Harman	Interaction with insect synapses	*377*
	Binding to DNA	*166*
Harmine	Inhibition of monoamine oxidase	*376*
	Interaction with insect synapses	*377*
	Binding to DNA	*378*
Harmol	Interaction with insect synapses	*377*
Isoboldine	Inhibition of adenylate cyclase	*361*

Melinone F	Binding to DNA	*379*
9-Methoxyellipticine	Inhibition of cytochrome *c* oxidase, interaction with phospholipids	*358*
	DNA intercalation	*359*
Norharman	Binding to DNA	*166*
Normelinone F	Binding to DNA	*379*
Pseudane/pseudene	Inhibition of mitochondrial electron transport	*380*
Quinine	Intercalation with DNA	*381*
	Modulation of ion channels	*382*
	Inhibition of glucose response in chemosensory cells	*383*
Reserpine	Quenching of singlet oxygen	*362*
	Inhibition of noradrenaline transport	*312*
Serotonin	Interaction with endogenous neurotransmitter, inhibition of pyridoxal kinase, aromatic amino acid decarboxylase, histamine methyltransferase	*221,376*
Skimmianine	Intercalation in DNA, photoaddition	*57*
Strychnine	Binding to glycine receptor	*364*
	Quenching of singlet oxygen	*362*
	Inhibition of muscle lactate dehydrogenase	*363*
Vincristine	Binding and dimerization of tubulin	*384–386*
	Inhibition of protein biosynthesis and DNA-dependent RNA polymerase	*387*
	Inhibition of intracellular transport	*388*
Tetrahydro-β-carboline	Inhibition of biogenic amine uptake	*389*
	Inhibition of monoamine oxidase	*389*
Toxiferine	Binding to acetylcholine receptor	*390*
Tryptamine	Inhibition of pyridoxal kinase, tyrosine–tRNA ligase	*376*
Tubocurarine	Binding to acetylcholine receptor	*391*
Vinblastine	Binding and dimerization of tubulin	*384–386*
	Inhibition of protein biosynthesis and DNA-dependent RNA polymerase	*387*
	Inhibition of intracellular transport	*388*
Vincamine	Quenching of singlet oxygen	*361*
Yohimbine	Adrenergic blocking agent	*312*

(*continued*)

TABLE IV (*Continued*)

Alkaloid	Effect	Ref.
Alkaloids derived from phenylalanine/tyrosine		
Alpinigenin	Inhibition of mitochondrial respiratory chain	*392*
Avicine	Intercalation with DNA	*393*
	Inhibition of reverse transcriptase, DNA polymerase	*393*
Berbamine	Interaction with plasma membranes	*394*
Berberine	Inhibition of reverse transcriptase	*395*
	Intercalation with DNA	*396–398*
	Inhibition of aldose reductase	*399*
	Inhibition of acetylcholinesterase, alcohol dehydrogenase, aldehyde reductase, diamine oxidase, tyrosine decarboxylase, RNA synthesis	*297*
Bicuculline	Modulation of GABA neurochemical activity	*364*
Bulbocapnine	Inhibition of peripheral dopamine receptors	*149*
Canadine	Inhibition of aldose reductase	*399*
Cepharanthine	Interaction with plasma membranes	*394*
Chelerythrine	Intercalation with DNA	*400*
	Inhibition of reverse transcriptase, alanine and aspartate aminotransferases	*259,401*
Chelidonine	Inhibition of reverse transcriptase	*401*
	Inhibition of microsomal monooxygenase	*402*
Chelilutine	Inhibition of DNA polymerase	*393*
Colchicine	Depolarization of microtubules, inhibition of urate-ribonucleotide phosphorylase	*376,441,442*
	Binding to tubulin, inhibition of microtubule polymerization	*384,448*
	Inhibition of intracellular transport	*388*
	Inhibition of RNA synthesis	*12*
Columbamine	Inhibition of butrylcholinesterase	*297*
Coptisine	Intercalation with DNA	*396*
	Inhibition of acetylcholinesterase, alcohol dehydrogenase	*297*

Coralyne	Intercalation with DNA	*386*
	Inhibition of reverse transcriptase, DNA polymerase	*403*
	Inhibition of catechol *O*-methyltransferase, alcohol dehydrogenase	*298*
	Inhibition of acetylcholinesterase, RNA polymerase, tRNA methyltransferase	*297*
Corlumine	Modulation of α-aminobutryric acid (GABA) neurochemical activity	*364*
Corysamine	Inhibition of alcohol dehydrogenase	*297*
Demethylpapaverine	Inhibition of aldose reductase	*399*
Dihydrochelerythrine	Inhibition of reverse transcriptase	*401*
Dihydrosanguinarine	Inhibition of reverse transcriptase	*401*
Domesticine	Inhibition of aldose reductase	*399*
Emetine	Inhibition of protein biosynthesis	*404*
Ephedrine	Modulation of noradrenaline release and noradrenaline receptors	*12,312*
Fagaronine	Intercalation with DNA	*88,400*
	Inhibition of reverse transcriptase, DNA polymerase	*403,404*
Galanthamine	Inhibition of acetylcholinesterase	*405*
Glaucine	Quenching of singlet oxygen	*361*
Isoboldine	Inhibition of aldose reductase	*399*
Jatrorrhizine	Inhibition of butyrylcholinesterase	*297*
Laudanosine	Modulation of glycine neurochemical activity	*364*
O-Methylfagaronine	Inhibition of reverse transcriptase	*403*
13-Methylpalmatine	Inhibition of reverse transcriptase	*297*
Nandazurine	Inhibition of aldose reductase	*399*
Nantenine	Inhibition of aldose reductase	*399*
Nitidine	Intercalation with DNA	*400*
	Inhibition of reverse transcriptase, DNA polymerase	*403*
	Inhibition of tRNA methyltransferase	*298*
	Inhibition of Na^+, K^+-ATPase	*298*
Nuciferine	Blocking of receptors for neurotransmitters (glutamate, aspartate, acetylcholine)	*260*

(*continued*)

TABLE IV (*Continued*)

Alkaloid	Effect	Ref.
Palmatine	Inhibition of reverse transcriptase	*395*
	Inhibition of aldose reductase	*399*
	Inhibition of acetylcholinesterase	*297*
Papaverine	Inhibition of aldose reductase	*297*
	Inhibition of GABA response in chemosensory cells	*383*
	Inhibition of glucose response in chemosensory cells	*383*
	Inhibition of phosphodiesterase	*406*
Salsolinol	Inhibition of monoamine oxidase	*389*
	Inhibition of biogenic amine uptake	*389*
Sanguinarine	Uncoupler of respiration and oxidative phosphorylation in mitochondria	*143*
	Inhibition of photosynthetic phosphorylation	*407*
	Inhibition of reverse transcriptase	*401*
	Inhibition of Na^+, K^+-ATPase	*259,408*
	Intercalation with DNA	*400,409*
Stepholidine	Inhibition of catecholamine uptake	*297*
Tetrahydroberberine	Inhibition of adenylate cyclase	*297*
Tetrahydroisoquinoline	Inhibition of catechol *O*-methyltransferase	*389*
	Inhibition of uptake of biogenic amines	*389*
Tetrahydropalmatine	Inhibition of catecholamine uptake	*297*
	Inhibition of respiratory chain in mitochondria	*392*
	Inhibition of aldose reductase	*399*
Tetrandrine	Interaction with plasma membrane	*243*
Thebaine	Inhibition of acetylcholinesterase	*260*
Tubulosine	Inhibition of protein biosynthesis	*404*
Tyramine	Inhibition of tyrosine–tRNA ligase	*376*
	Modulation of noradrenaline release	*12*
Polyhydroxy alkaloids		
Alexine	Inhibition of myrosinase/glucosinate hydrolysis at 64–860 μM	*212,410,411*

Castanospermine	Inhibition of glucosidases	*150*
	Inhibition of myrosinase	*412*
	Inhibition of insect disaccharidases	*197*
	Inhibition of myrosinase/glucosinate hydrolysis	*212,410,411*
Deoxynorjirimycin	Inhibition of glucosidase	*150,212*
1-Deoxynorjirimycin	Inhibition of myrosinase/glucosinate hydrolysis	*212,410*
1,5-Dideoxy-1,5-imino-D-mannitol	Inhibition of α-mannosidase, trehalase	*212,410*
2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine	Inhibition of myrosinase/glucosinate hydrolysis	*212,410*
	Inhibition of glucosidase	*150,212*
	Inhibition of trehalase, invertase	*212*
6-Epicastanospermine	Inhibition of α-glucosidase	*411*
Homonorjirimycin	Inhibition of myrosinase/glucosinate hydrolysis	*212,410,411*
	Inhibition of glucosidase	*413*
Nojirimycin	Inhibition of α-amylase, β-fructofuranosidase, α-glucosidase	*376*
Swainsonine	Inhibition of α-mannosidase, mannosidase II	*376,414*
Purine alkaloids		
Caffeine	Inhibition of cAMP phosphodiesterase, dATP(dGTP)–DNA purinetransferase	*202,376*
Theophylline	Inhibition of cAMP phosphodiesterase	*202,415*
Quinolizidine alkaloids		
Angustifoline	Inhibition of Phe–tRNA binding to ribosomes	*417*
	Inhibition of Phe–tRNA binding and elongation	*99,422*
Cytisine	Inhibition of Phe–tRNA binding	*56*
	Inhibition of *in vitro* translation (wheat germ)	*56*
13-Hydroxylupanine	Inhibition of Phe–tRNA binding to ribosomes	*417*
	Inhibition of *in vitro* translation (wheat germ)	*56*
	Inhibition of Phe–tRNA binding and elongation	*99,422*
Lupanine	Inhibition of Phe–tRNA binding to ribosomes	*417*
	Inhibition of Phe–tRNA binding and elongation	*99,422*
	Inhibition of *in vitro* translation (wheat germ)	*56*
Matrine	Inhibition of neural glutamate action	*420*

(*continued*)

TABLE IV (*Continued*)

Alkaloid	Effect	Ref.
17-Oxosparteine	Inhibition of Phe–tRNA binding	*56*
	Inhibition of *in vitro* translation (wheat germ)	*56*
Sparteine	Modulation of K^+ channels	*416,418*
	Inhibition of Phe–tRNA binding to ribosomes	*417*
	Inhibition of GABA response in chemosensory cells	*383*
	Increase in insulin release in β cells	*419*
	Inhibition of aminoacyl-tRNA synthase	*421*
	Inhibition of Phe–tRNA binding and elongation	*99,422*
	Inhibition of *in vitro* translation (wheat germ)	*56*
13-Tigloyloxylupanine	Inhibition of Phe–tRNA binding	*56*
	Inhibition of *in vitro* translation (wheat germ)	*56*
Pyrrolizidine alkaloids		
2,3-Dehydropyrrolizidines	Alkylation of DNA and proteins	*425,426*
Heliotrine	Inhibition of acetylcholinesterase	*424*
Monocrotaline	Modulation of pulmonary Na^+/K^+ pumps	*423*
Steroidal alkaloids		
Batrachotoxin (frog)	Activation of Na^+ channels	*427,428*
Cevadine	Depolarizes membranes	*234,429*
Chaconine	Disruption of biomembranes by cholesterol binding	*430,433*
	Inhibition of acetylcholinesterase	*431,432*
Commersonine	Inhibition of acetylcholinesterase	*432*
Demissine	Inhibition of acetylcholinesterase	*432*
Isorubijervine	Blocking of action potential	*234*
Muldamine	Blocking of action potential	*234*
Protoveratrines A,B	Inhibition of inactivation of Na^+ channels, depolarization of membranes	*234,259*
Solacongestidine	Inhibition of cholesterol biosynthesis	*434*
Solamargine	Disruption of biomembranes	*435*
	Binding of cholesterol, hemolysis	*435*
	Inhibition of acetylcholinesterase	*431*

Solanine	Complexing with sterols, membrane disruption	*430,433*
	Inhibition of acetylcholinesterase	*432*
	Inhibition of GABA response in chemosensory cells	*383*
Solanidine	Inhibition of acetylcholinesterase	*432*
Solasonine	Synergistic with solamargine	*435*
	Binding of cholesterol	*435*
Tomatine	Inhibition of GABA response in chemosensory cells	*383*
Veratramine	Blocking of action potential	*234*
Veratridine	Activation of Na^+ channels	*234,427*
Tropane alkaloids		
Atropine	Quenching of singlet oxygen	*361*
	Binding to muscarinergic acetylcholine receptor	*312*
Cocaine	Binding/inhibition of dopamine uptake carrier	*12,436*
Miscellaneous alkaloids		
Aconitine	Activation of Na^+ channels, no repolarization	*259,427*
Amanitin	Inhibition of RNA polymerases II and III (transcription)	*376*
Anabaseine	Modulation of acetylcholine receptor	*230*
Arecoline	Binding to acetylcholine receptor	*437*
Batrachotoxin	Increase of Na^+ permeability	*234,388*
Capsaicine	Inhibition of Na^+,K^+-ATPase, glucose transport	*439*
	Inhibition of mitochondrial electron transport	*440*
Cassaine	Inhibition of Na^+,K^+-ATPase	*408*
Cryptopleurine	Inhibition of protein biosynthesis	*404,444*
Cycasin (=methylazoxymethanol)	Alkylation of DNA	*343*
Dendrobine	Modulation of glycine neurochemical activity	*364*
DIMBOA/MBOA	Inhibition of energy transfer in mitochondria	*445*
	Inhibition of energy transfer in chloroplasts	*106*
	Binding to auxin receptors in plants	*106*
	Inhibition of ATPase	*106*
	Inactivation of SH groups	*446,447*
	Inactivation of amino groups	*446,448*

(*continued*)

TABLE IV (*Continued*)

Alkaloid	Effect	Ref.
Gephyrotoxin	Inhibition of acetylcholine receptor	*428*
Harringtonine	Inhibition of protein biosynthesis	*449*
Homoharringtonine	Inhibition of protein biosynthesis	*390*
Hemanthamine	Inhibition of protein biosynthesis	*390*
Hippeastrine	Inhibition of DNA polymerase	*148*
Histrionicotoxin	Inhibition of K^+ channels	*428*
Irehdiamine	Disturbance of membrane permeability	*390*
Isoharringtonine	Inhibition of protein biosynthesis	*390*
Lycorine	Inhibition of DNA polymerase	*148*
	Inhibition of protein biosynthesis, binding to 60 S subunit	*259,390*
Maitoxin	Activation of Ca^{2+} channels	*259*
Malouetine	Disturbance of membrane permeability	*390*
Maytansine	Binding to microtubules	*390*
Maytansinine	Inhibition of cell division	*450*
Methyllycaconitine	Cholinergic agonist (insect nicotine receptor)	*200*
C15-2,6-methylpiperidine	Inhibition of mitochondrial electron transport	*228*
	Inhibition of Na^+,K^+-ATPase	*438*
Muscarine	Binding to acetylcholine receptor	*312*
Narciclasine	Inhibition of protein biosynthesis	*451*
Nicotine	Activation of acetylcholine receptor	*200,312*
	Inhibition of carotenoid biosynthesis	*452*
	Induction of vacuole formation in *Puccinia*	*453*
	Quenching of singlet oxygen	*361*
Ochratoxin	Inhibition of glucose transport	*259*
Olivacine	Intercalation with DNA	*454*
Palytoxin	Increase of Na^+/K^+ permeability, hemolysis	*259*
Pilocarpine	Binding to muscarinic acetylcholine receptor	*259*
Pretazettine	Inhibition of protein biosynthesis	*390*
Pseudolycorine	Inhibition of protein biosynthesis	*390*

Psilocin/psilocybin	Interaction with serotonin receptor (hallucinogen)	*312*
Pumiliotoxin B	Inhibition of Ca^{2+} channels	*428*
Pumiliotoxin C	Inhibition of acetylcholine receptor	*428*
Saxitoxin	Inhibition of Na^+ channels	*234,259*
Solenopsine	Inhibition of Na^+,K^+-ATPase and mitochondrial respiratory chain	*259*
Streptonigrine	Inhibition of reverse transcriptase	*455*
Taxol	Promotion of polymerization of tubulin, polyploidization	*443*
Tetrodotoxin	Inhibition of Na^+ channels	*259,388*
Trigonelline	Promotion of cell arrest in G_2 of cell cycle in plants	*456,457*
Tylocrebrine	Inhibition of protein biosynthesis	*390*
Tylocrepine	Inhibition of protein biosynthesis	*404*
Tylophorine	Inhibition of protein biosynthesis	*444*
Xestoaminol A, C	Inhibition of reverse transcriptase	*112*
Antibiotics		
Actinobolin	Inhibition of protein biosynthesis	*149*
Actinomycin	Intercalation in DNA, inhibition of RNA synthesis	*437*
Amphotericin B	Interaction with membrane sterols, formation of membrane channels	*312*
Bacitracin	Inhibition of dolichol metabolism, geranyltransferase	*376*
Bleomycin	DNA binding and cleavage	*437*
	Inhibition of DNA polymerase, RNA polymerase, protein-glutamine γ-glutamyltransferase	*376*
Calcimycin	Ca^{2+} ionophore in mitochondria	*149*
Calichemycin	DNA binding and cleavage	*437*
Cephalosporin	Inhibition of transpeptidase	*312*
Cephamycin	Inhibition of transpeptidase	*312*
Chloramphenicol	Inhibition of translation	*312*
Cycloheximide	Inhibition of translation	*312*
Cytochalasin B	Inhibition of glucose transport, blocking of contractile microfilaments	*149,376,388*
Daunorubicin	Inhibition of RNA polymerase, procollagen-proline,2-oxoglutarate 4-dioxygenase, intercalation with DNA	*312,376*
Demeclocyclin	Inhibition of translation	*312*

(*continued*)

TABLE IV (*Continued*)

Alkaloid	Effect	Ref.
Doxorubicin	Inhibition of RNA polymerase, intercalation into DNA	*312,376*
Erythromycin	Inhibition of translation	*312*
Esparamycin	DNA binding and cleavage	*437*
Gentamycin	Inhibition of translation	*312*
Gramicidin	Formation of ion channels (Na^+, K^+, H^+) in plasma membrane	*312*
Josamycin	Inhibition of translation	*312*
Kanamycin	Inhibition of translation	*312*
Lincomycin	Inhibition of translation	*312*
Mitomycin C	Alkylation of DNA, inhibition of replication	*312,437*
Neomycin	Inhibition of 1-phosphatidylinositol-4,5-biphosphate phosphodiesterase Inhibition of translation	*312,376*
Novobiocin	Inhibition of DNA topoisomerase	*376*
Nystatin A	Interaction with membrane sterols, formation of membrane channels	*312*
Oxytetracyclin	Inhibition of translation	*312*
Penicillins and β-lactam derivatives	Inhibition of transpeptidase (murein formation)	*312*
Polymyxins A–E	Inhibition of protein kinase C, increase of membrane permeability	*312,376*
Rifampicin	Inhibition of DNA polymerase	*376*
Rifamycin	Inhibition of RNA and DNA polymerases	*376*
Spectinomycin	Inhibition of translation	*312*
Spiramycin	Inhibition of translation	*312*
Streptomycin	Inhibition of translation	*312*
Tetracyclin	Inhibition of translation	*312*
Tobramycin	Inhibition of translation	*312*
Tyrothricin	Modulation of membrane permeability	*312*
Vancomycin	Inhibition of peptidoglycan biosynthesis	*312*

a. Cellular Targets

Nucleic Acids. DNA, the macromolecule which holds all the genetic information for the life and development of an organism, is a highly vulnerable target. It is not surprising that a number of secondary metabolites have been selected during evolution which interact with DNA or DNA-processing enzymes. Some alkaloids bind to or intercalate with DNA/RNA (Table IV) and thus affect replication or transcription, or cause mutations, leading to malformations or cancer (Table V): 9-methoxyellipticine, dictamnine, ellipticine, harmane alkaloids, melinone F, quinine and related alkaloids, skimmianine, avicine, berberine, chelerythrine, coptisine, coralyne, fagaronine, nitidine, sanguinarine, pyrrolizidine alkaloids (PAs), cycasin, olivacine, etc. Many of the intercalating molecules are planar, hydrophobic molecules that fit within the stacks of AT and GC base pairs.

Other alkaloids act at the level of DNA and RNA polymerases, such as vincristine, vinblastine, avicine, chelilutine, coralyne, fagaronine, nitidine, amanitine, hippeastrine, and lycorine, thus impairing the processes of replication and transcription. Whereas these toxins usually cause a rapid reaction, some alkaloids cause long-term effects in vertebrates in that they are mutagenic or carcinogenic (Table V). Besides basic data obtained in *Salmonella* or *Drosophila,* there are a few reports which illustrate the potent mutagenic effect of alkaloids on vertebrates. Anagyrine, anabasine, and coniine cause "crooked calf disease" if pregnant cows or sheep feed on these alkaloids during the first period of gestation (*329,341,348,349,351,352*). The offspring born show strong malformation of the legs. Some of the steroid alkaloids (e.g., cyclopamine, jervine, and veratrosine), which are produced by *Veratrum* species, cause the formation of a central large cyclopean eye (*329-331*), an observation that was probably made by the ancient Greeks and thus led to the mythical figure of the cyclops. It is likely that any herbivore which regularly feeds on plants containing these alkaloids will suffer from reduced productivity and reduced fitness in the long term. In effect, the plants which contain these alkaloids are usually avoided by vertebrate herbivores.

Another long-term effect caused by alkaloids with carcinogenic properties has been discovered only recently (Tables IV and V). The alkaloid aristolochic acid, which is produced by plants of the genus *Aristolochia,* is carcinogenic. The mechanism of action of this alkaloid is believed to be similar to the well-known carcinogen nitrosamine (*344,345*), because of its NO_2 group. Pyrrolizidine alkaloids and their *N*-oxides, which are abundantly produced by members of the Asteraceae and Boraginaceae but also occur in the families Apocynaceae, Celestraceae, Elaeocarpaceae, Euphorbiaceae, Fabaceae, Orchidaceae, Poaceae, Ranunculaceae, Rhizo-

TABLE V

MUTAGENIC OR CARCINOGENIC ACTIVITY OF ALKALOIDS

Alkaloid	Effect	ED_{50}	Ref.
Alkaloids derived from tryptophan			
Vinblastine/vincristine	Fetal malformation in hamster	—	*324*
	Skeletal, ocular, and CNS malformations in man	—	*325*
Vaocristine	Mutagenic in yeast	50–100 μg/ml	*284*
Quinoline alkaloids			
Dictamnine	Induction of revertants in *Salmonella typhimurium* (ST)	5–20 μg/plate	*326*
	Frameshift induction in *E. coli*	—	*327*
Evolitrine	Induction of revertants in ST	5–20 μg/plate	*326*
Fagarine	Induction of revertants in ST	5–20 μg/plate	*326*
	Induction of sister-chromatid exchanges	—	*328*
Flindersiamine	Induction of revertants in ST	5–20 μg/plate	*326*
Kokusaginine	Induction of revertants in ST	5–20 μg/plate	*326*
Maculine	Induction of revertants in ST	5–20 μg/plate	*326*
Maculosidine	Induction of revertants in ST	5–20 μg/plate	*326*
Pteleine	Induction of revertants in ST	5–20 μg/plate	*326*
Skimmianine	Induction of revertants in ST	5–20 μg/plate	*326*
Alkaloids derived from phenylalanine/tyrosine			
Aristolochic acid	Carcinogenic, mutagenic	—	*344,345*
	Mutagenic in ST	—	*346*
Berberine	Mutagenic	—	*297*
Colchicine	Mutagenic in *Lolium*	—	*347*
Thebaine	Teratogenic in hamster, congenital malformations	—	*260*
Steroidal alkaloids			
11-Deoxojervine (cyclopamine)	Teratogenic, cyclopian malformation	—	*329,330*
Jervine	Teratogenic, cyclopian malformation	—	*329,330*
Solanine	Teratogenic in chick embryo, rumplessness	—	*261*

Solasodine	Teratogenic, malformations in hamster embryos	—	*330,331*
Veratrosine	Teratogenic, cyclopian malformation	—	*329,330*
Pyrrolizidine alkaloids			
7-Acetylintermedine	Mutagenic in *Drosophila*	Minimal 0.01 m*M*	*333*
7-Acetyllycopsamine	Mutagenic in *Drosophila*	Minimal 0.025 m*M*	*333*
Heliotrine	Mutagenic in *Drosophila*	Minimal 0.025 m*M*	*332,333*
	Abdominal abnormalities in *Drosophila*	10 μM	*334*
Indicine	Mutagenic in *Drosophila*	Minimal 1 m*M*	*333*
Integerrimine	Chromosome damage in mouse bone marrow cells	18–38 mg/kg	*336*
	Teratogenicity, mutagenicity	—	*336*
	Mutagenic in *Drosophila*	—	*337*
Intermedine	Mutagenic in *Drosophila*	Minimal 0.5 m*M*	*333*
Jacoline	Mutagenic in *Drosophila*	Minimal 0.1 m*M*	*333*
Lasiocarpine	Mutagenic in ST	—	*338*
Lycopsamine	Mutagenic in *Drosophila*	Minimal 1 m*M*	*333*
Monocrotaline	Mutagenic in *Drosophila*	1 m*M*	*332*
	Mutagenic in *Drosophila*	Minimal 0.0025 m*M*	*333*
Retrorsine	Mutagenic in *Drosophila*	Minimal 0.05 m*M*	*333*
Senecionine	Mutagenic in *Drosophila*	Minimal 0.005 m*M*	*333*
Seneciphylline	Mutagenic in *Drosophila*	>10 μM	*335*
Senkirkine	Mutagenic in *Drosophila*	>10 μM	*335*
	Mutagenic in *Drosophila*	Minimal 0.005 m*M*	*333*
Symphytine	Mutagenic in *Drosophila*	Minimal 0.1 m*M*	*333*
PAs general	Chromosome breakage/rearrangements in root tips	—	*339*
	Chromosome breakage in leukocytes	—	*340*
Quinolizidine alkaloids			
Anagyrine	Teratogenic, congenital malformations in calves ("crooked calf disease")	—	*329,341*
Cytisine	Teratogenic in chicks and rabbits	—	*341*

(*continued*)

TABLE V (*Continued*)

Alkaloid	Effect	ED_{50}	Ref.
Miscellaneous alkaloids			
Anabasine	Teratogenic, crooked calf disease	—	*351,352*
Arecaidine	Chromatid exchanges in bone marrow cells	—	*356*
Caffeine	Chromatid exchanges	—	*354*
Capsaicin	Mutagenic	—	*355*
Coniceine	Teratogenic, congenital skeletal malformation in pigs	—	*350*
Coniine	Teratogenic, crooked calf disease	—	*348,349*
Cryptopleurine	Chromosome breaks in *Drosophila*	—	*332*
Cycasin	Mutagenic, carcinogenic	—	*342,343*
DIBOA, DIMBOA	Mutagenic in ST	—	*106*
Theobromine	Genotoxicity	—	*353*
	Chromatid exchanges	—	*354*

phoraceae, Santalaceae, Sapotaceae, and Scrophulariaceae (*502*) (~3% of higher plants produce these alkaloids), have mutagenic and carcinogenic properties, provided the molecules have the 1,2-dehydro-1-hydroxymethyl-pyrrolizidine structure and are esterified (*425,426*). After oral intake, the *N*-oxides are reduced by bacteria in the gut. The lipophilic alkaloid base is resorbed and transported to the liver, where it is "detoxified" by microsomal enzymes. As a result, a reactive alkylating agent is generated, which can be considered as a pyrrolopyrrolidine. The alkaloid can then cross-link DNA and RNA and thus cause mutagenic or carcinogenic effects (especially in the liver) (*502*). Thus, pyrrolizidine alkaloids represent highly evolved and sophisticated antiherbivore compounds, which utilize the widespread and active detoxification system of the vertebrate liver.

The PA story is very intriguing, since it shows how ingenious Nature was in the "arms race." The herbivores invented detoxifying enzymes, and Nature the compound which is activated by this process. A herbivore feeding on PA-containing plants will eventually die, usually without reproducing properly. Only those individuals which carefully avoid the respective bitter-tasting plants maintain their fitnes and thus survive. The protection due to PA can easily be seen on meadows, where *Senecio* and other PA-containing plants are usually not taken by cows and sheep, at least as long other food is available.

Protein biosynthesis. Protein biosynthesis is essential for all cells and thus another important target. Indeed, a number of alkaloids have already been detected (although few have been studied in this context) that inhibit protein biosynthesis *in vitro* (Table IV), such as vincristine, vinblastine, emetine, tubulosine, tyramine, sparteine, lupanine and other quinolizidine alkaloids, cryptopleurine, harringtonine, homoharringtonine, haemanthamine, isoharringtonine, lycorine, narciclasine, pretazettine, pseudolycorine, tylocrebrine, tylophorine, and tylocrepine. For lupine alkaloids, it was determined that the steps which are inhibited are the loading of acyl-tRNA with amino acids, as well as the elongation step. The inhibitory activity was strongly expressed in heterologous systems, that is, protein biosynthesis in the producing plants, such as lupines, was not affected (*503*).

Electron chains. The respiratory chain and ATP synthesis in mitochondria demand the controlled flux of electrons. This target seems to be attacked by ellipticine, pseudane, pseudene, alpinigenine, sanguinarine, tetrahydropalmatine, CH_3-$(CH_2)_{14}$-2,6-methyl-piperidines, capsaicin, the hydroxamic acid DIMBOA, and solenopsine. As mentioned before, however, only a few alkaloids have been evaluated in this context (Table V).

Biomembranes and transport processes. A cell can operate only when it is enclosed by an intact biomembrane and by a complex compartmenta-

tion that provides separated reaction chambers. Because biomembranes are impermeable for ions and polar molecules, cells can prevent the uncontrolled efflux of essential metabolites. The controlled flux of these compounds across biomembranes is achieved by specific transport proteins, which can be ion channels, pores, or carrier systems.

These complex systems are also targets of many natural products (Table IV). Disturbance of membrane stability is achieved by 9-methoxyellipticine, ellipticine, berbamine, cepharanthine, tetrandrine, steroidal alkaloids, irehdiamine, and malouetine. Steroidal alkaloids, such as solanine and tomatine, which are present in many members of the Solanaceae, can complex with cholesterol and other lipids of biomembranes; cells are thus rendered leaky.

Cells carefully control the homeostasis of their ion concentrations by the action of ion channels (Na^+,K^+, Ca^{2+} channels) and through Na^+,K^+-ATPase and Ca^{2+}-ATPase. These channels and pumps are involved in signal transduction, active transport processes, and neuronal and neuromuscular signaling. Inhibition of transport processes (ion channels, carriers) is achieved by (Table IV) acronycine, ervatamine, harmaline, quinine, reserpine, colchicine, nitidine, salsolinol, sanguinarine, stepholidine, caffeine, sparteine, monocrotaline, steroidal alkaloids, aconitine, capsaicine, cassaine, maitoxin, ochratoxin, palytoxin, pumiliotoxin, saxitoxin, solenopsine, and tetrodotoxin.

A special class of ion channels in the central nervous system and involved in neuromuscular signal transfer are coupled with receptors of neurotransmitters such as noradrenaline (NA), serotonin, dopamine, glycine, and acetylcholine (ACH). We can distinguish two types. Type 1 is a ligand-gated channel (i.e., a receptor), which is part of an ion–channel complex, such as the nicotinergic ACH-receptor. In Type 2 the receptor is an integral protein. When a neurotransmitter binds, the receptor changes its conformation and induces a conformational change in an adjacent G-protein molecule, which consists of three subunits. The α subunit then activates the enzyme adenylate cyclase, which in turn produces cAMP from ATP. The cAMP molecule is a second messenger which activates protein kinases or ion channels directly, which in turn open for milliseconds (e.g., the muscarinergic ACH receptor).

A number of alkaloids are known whose structures are more or less similar to those of endogenous neurotransmitters. Targets can be the receptor itself, the enzymes which deactivate neurotransmitters, or transport processes, which are important for the storage of the neurotransmitters in synaptic vesicles. Alkaloids relevant here include (Table IV) brucine, ergot alkaloids, eseridine, serotonin, physostigmine, gelsemine, β-carboline alkaloids, strychnine, yohimbine, berberine, bicuculline, bulbocapnine, columbamine, coptisine, coralyne, corlumine, ephedrine, ga-

lanthamine, laudanosine, nuciferine, palmatine, papaverine, thebaine, cytisine and other quinolizidine alkaloids, heliotrine, chaconine and other steroidal alkaloids, cocaine, atropine, scopolamine, anabaseine, arecoline, dendrobine, gephyrotoxin, histrionicotoxin, methyllycaconitine, muscarine, nicotine, pilocarpine, psilocin, psilocybin, morphine, mescaline, and reserpine. A number of these alkaloids are known hallucinogens, which certainly decrease the fitness of an herbivore feeding on them regularly.

Cytoskeleton. Many cellular activities, such as motility, endocytosis, exocytosis, and cell division, rely on microfilaments and microtubules. A number of alkaloids have been detected which can interfere with the assembly or disassembly of microtubules (Table IV), namely, vincristine, vinblastine, colchicine, maytansine, maytansinine, and taxol.

Colchicine, the major alkaloid of *Colchicum autumnale* (Liliaceae), inhibits the assembly of microtubules and the mitotic spindle apparatus. As a consequence, chromosomes are no longer separated, leading to polyploidy. Whereas animal cells die under these conditions, plant cells maintain their polyploidy, a trait often used in plant breeding because polyploidy leads to bigger plants. Because of this antimitotic activity, colchicine has been tested as an anticancer drug; however, it was abandoned because of its general toxicity. The derivative colcemide is less toxic and can be employed in the treatment of certain cancers (*312*). Also, cellular motility is impaired by colchicine; this property is exploited in medicine in the treatment of acute gout, in order to prevent the migration of macrophages to the joints. For normal cells, and thus for herbivores, the negative effects can easily be anticipated, and colchicine is indeed a very toxic alkaloid which is easily resorbed because of its lipophilicity. *Colchicum* plants are not attacked by herbivores to any substantial degree (*185*).

Another group of alkaloids with antimitotic properties are the bisindole alkaloids, such as vinblastine and vincristine, which have been isolated from *Catharanthus roseus* (Apocynaceae). These alkaloids also bind to tubulin (*312*). Both alkaloids are very toxic, but are nevertheless important drugs for the treatment of some leukemias.

From *Taxus baccata* (Taxaceae) the alkaloid taxol has been isolated. Taxol also affects the architecture of microtubules in inhibiting their disassembly (*312*). Nonalkaloidal compounds to be mentioned in this context include the lignan podophyllotoxin (*312*). In conclusion, any alkaloid which impairs the function of microtubules is likely to be toxic, because of their importance for a cell, and, from the point of view of defense, a well-working and well-shaped molecule.

Enzyme inhibition. The inhibition of metabolically important enzymes is a wide field that cannot be discussed in full here (see Table IV). Briefly, inhibition of cAMP metabolism (which is important for signal transduction

and amplifications in cells), namely, inhibition of adenylate cyclase by anonaine, isoboldine, tetrahydroberberine and inhibition of phosphodiesterase by 1-ethyl-β-carboline, β-carboline-1-propionic acid, papaverine, caffeine, theophylline, and theobromine are some examples. Inhibition of hydrolases, such as glucosidase, mannosidase, trehalase, and amylase, is specifically achieved by some alkaloids (Table IV). Castanospermine, swainsonine, and other polyhydroxyalkaloids are examples.

b. Action at Organ Level. Whereas the activities mentioned before are more or less directed to molecular targets present in or on cells, there are also some activities that function at the level of organ systems or complete organisms, although, ultimately, they have molecular targets, too.

Central nervous system and neuromuscular junction. A remarkable number of alkaloids interfere with the metabolism and activity of neurotransmitters in the brain and nerve cells, a fact known to man for a thousand years (Table IV). The cellular interactions have been discussed above. Disturbance of neurotransmitter metabolism impairs sensory faculties, smell, vision, or hearing, or they may produce euphoric or hallucinogenic effects.

A herbivore that is no longer able to control its movements and senses properly has only a small chance of survival in Nature, because it will have accidents (falling from trees, or rocks, or into water) and be killed by predators. Thus euphoric and hallucinogenic compounds, which are present in a number of plants, and also in fungi and the skin of certain toads, can be regarded as defense compounds. Some individuals of *Homo sapiens* use these drugs just because of their hallucinogenic properties, but here also it is evident that long-term use reduces survival and fitness dramatically.

The activity of muscles is controlled by ACH and NA. It is plausible that an inhibition or activation of neurotransmitter-regulated ion channels will severely influence muscular reactivity and thus the mobility or organ function (heart, blood vessels, lungs, gut) of an animal. In the case of inhibition, muscles will relax; in the case of overstimulation, muscles will be tense or in tetanus, leading to a general paralysis.

Alkaloids which activate neuromuscular action (so-called parasympathomimetics) include nicotine, arecoline, physostigmine, coniine, cytisine, and sparteine. Inhibitory (or parasympatholytic) alkaloids include hyoscyamine and scopolamine, (see above) (*312*). Skeletal muscles as well as muscle-containing organs, such as lungs, heart, circulatory system, and gut, and the nervous system are certainly very critical targets. The compounds are usually considered to be strong poisons, and it is obvious that

they serve as chemical defense compounds against herbivores, since a paralyzed animal is easy prey for predators or, if higher doses are ingested, will die directly (compare LD_{50} values in Table II).

Inhibition of digestive processes. Food uptake can be reduced by a pungent or bitter taste in the first instance, as mentioned earlier. The next step may be the induction of vomiting, diarrhea, or the opposite, constipation, which negatively influences digestion in animals. The ingestion of a number of allelochemicals such as emetine, lobeline, morphine, and many other alkaloids causes these symptoms (*312*).

Another mode of interference would be the inhibition of carriers for amino acids, sugars, or lipids, or of digestive enzymes. Relevant alkaloids are the polyhydroxyalkaloids, such as swainsonine, deoxynorjirimycin, and castanospermine, that inhibit hydrolytic enzymes, such as glucosidase, galactosidase, trehalase (trehalose is a sugar in insects which is hydrolyzed by trehalase), and mannosidase selectively (Table IV).

Modulation of liver and kidney function. Nutrients and xenobiotics (such as secondary metabolites) are transported to the liver after resorption in the intestine. In the liver, the metabolism of carbohydrates, amino acids, and lipids takes place with the subsequent synthesis of proteins and glycogen. The liver is also the main site for detoxification of xenobiotics. Lipophilic compounds, which are easily resorbed from the diet, are often hydroxylated and then conjugated with a polar, hydrophilic molecule, such as glucuronic acid, sulfate, or amino acids (*312*). These conjugates, which are more water soluble, are exported via the blood to the kidney, where they are transported into the urine for elimination.

Both liver and kidney systems are affected by a variety of secondary metabolites, and the pyrrolizidine alkaloids have been discussed earlier (Tables IV and V). The alkaloids are activated during the detoxification process, and this can lead to liver cancer. Also, many other enzyme or metabolic inhibitors (e.g., amanitine), discussed previously, are liver toxins.

Many alkaloids and other allelochemicals are known for their diuretic activity (*312*). For an herbivore, an increased diuresis would also mean an augmented elimination of water and essential ions. Since Na^+ is already limited in plant food (an antiherbivore device?), long-term exposure to diuretic compounds would reduce the fitness of an herbivore substantially.

Disturbance of reproduction. Quite a number of allelochemicals are known to influence the reproductive system of animals, which ultimately reduces their fitness and numbers. Antihormonal effects could be achieved by mimicking the structure of sexual hormones. These effects are not known for alkaloids yet, but have been confirmed for other natural products. Estrogenic properties have been reported for coumarins, which di-

merize to dicoumarols, and isoflavones (*4,17*). Insect molting hormones, such as ecdysone, are mimicked by many plant sterols, which include ecdysone itself, such as in the fern *Polypodium vulgare*, or azadirachtin from the neem tree (*4,17*). Juvenile hormone is mimicked by a number of terpenes, present in some Coniferae. Spermatogenesis is reduced by gossypol from cottonseed oil (*17*).

The next target is the gestation process itself. As outlined above, a number of alkaloids are mutagenic and lead to malformation of the offspring or directly to the death of the embryo (Table V). The last step would be the premature abortion of the embryo. This dramatic activity has been reported for a number of allelochemicals, such as mono- and sesquiterpenes and alkaloids. Some alkaloids achieve this by the induction of uterine contraction, such as the ergot and lupine alkaloids (*312*).

The antireproductive effects are certainly widely distributed, but they often remain unnoticed under natural conditions. Nevertheless, they are defense strategies with long-term consequences.

Blood and circulatory system. All animals need to transport nutrients, hormones, ions, signal compounds, and gas between the different organs of the body, which is achieved by higher animals through blood in the circulatory system. Inhibitors of the driving force for this process, the heart muscle, have already been discussed. However, the synthesis of red blood cells is also vulnerable and can be inhibited by antimitotic alkaloids such as vinblastine or colchicine (*312*).

Some allelochemicals have hemolytic properties, such as saponins. If resorbed, these compounds complex membrane sterols and make the cells leaky. Steroidal alkaloids from *Solanum* or *Veratrum* species display this sort of activity as well as influencing ion channels (Table IV).

Allergenic effects. A number of secondary metabolites influence the immune system of animals, such as coumarins, furanocoumarins, hypericin, and helenalin. Common to these compounds is a strong allergenic effect on those parts of the skin or mucosa that have come into contact with the compounds (*4,17,312*). Activation or repression of the immune response is certainly a target that was selected during evolution as an antiherbivore strategy. The function of alkaloids in this context is hardly known.

This selection of alkaloid activities, though far from complete, clearly shows that many alkaloids inhibit central processes at the cellular, organ, or organismal level, an important requisite for a chemical defense compound. However, most of the potential targets for the 10,000 alkaloids known at present remain to be established. If no activity has been reported, it often means that nobody looked into this question scientifically, and not that a particular alkaloid is without a certain biological property.

Summarizing this section, it is safe to assume that most alkaloids can affect animals and thus herbivores significantly.

B. Plant–Microbe Interactions

Dead plants easily rot due to the action of bacteria and fungi, whereas metabolically active, intact plants are usually healthy and do not decay (*7*). How is this achieved? The aerial organs of terrestrial plants have epidermal cells that are covered by a more or less thick cuticle, which consists of waxes, alkanes, and other lipophilic natural products (*4,7*). This cuticle layer is water repellent and chemically rather inert, and it thus constitutes an important penetration barrier for most bacteria and fungi. In perennial plants and in roots we find another variation of this principle in that plants often form resistant bark tissues.

The only way for microbes to enter a healthy plant is via the stomata or at sites of injury, inflicted by herbivory, wind, or other accidents. At the site of wounding, plants often accumulate suberin, lignin, callose, gums, or other resinous substances which close off the respective areas (*4,17*). In addition, antimicrobial agents are produced such as lysozyme and chitinase, lytic enzymes stored in the vacuole which can degrade bacterial and fungal cell walls, protease inhibitors which can inhibit microbial proteases, or secondary metabolites with antimicrobial activity.

Secondary metabolites have been routinely screened for antimicrobial activities by many researchers, since the corresponding assays are relatively easy to perform. These studies have usually been directed toward a pharmaceutical application, and they often employ the routine methods for screening microbial or fungal antibiotics. It may happen that these tests do not detect an antibacterial activity of a compound because the wrong test species or a nonrelevant concentration was assayed. In the pharmaceutical context we search for very active compounds which can be employed at low concentrations. Therefore, the higher concentrations, which would be more meaningful ecologically, are often not tested. These precautions have to be kept in mind when screening the literature for data on the antimicrobial activity of alkaloids.

Secondary compounds known for their antimicrobial activity include many phenolics (e.g., flavonoids, isoflavones, and simple phenolics), glucosinolates, nonproteinogenic amino acids, cyanogenic glycosides, acids, aldehydes, saponins, triterpenes, mono- and disesquiterpenes, and last but not least, alkaloids (*4,17,42,149,312*).

In Table VI 183 alkaloids are tabulated for which antibacterial activities have been detected. The alkaloids usually affect more gram-positive than gram-negative bacteria. Especially well represented are alkaloids which

TABLE VI

ALKALOIDS WITH ANTIBACTERIAL PROPERTIES

Alkaloid	Active against		Test	Concentration tested (μg/m)	MIC (mg/ml)	ED_{50} (mg/ml)	Ref.
	Gram (+)	Gram (−)					
Alkaloids derived from tryptophan							
Affinisine	+	+	AL	1	1000		*50*
Ajmalicine		+	AD	15			*51*
Apparicine	+	+	AD	12			*52*
Aspidospermine	+	+	AL	1	1000		*50*
Bisnordihydrotoxiferine	+	+	AD		270–3000		*53*
	+	+	AL		1–100		*54*
Bisnordihydrotoxiferine *N*-oxide	+		AD	2			*53*
Borreverine	+	+	AL		2–400		*55*
Brevicolline	+						*57*
5-Bromo-*N*,*N*-dimethylaminoethyltryptamine	+	+	AD				*72*
Brucine	−		AD	5			*53*
	+		LD			1	*56*
Bufotenine	+	+	LD				*113*
Canthin-6-one	+	+	AD		12–100		*50,58*
Caracurine V	+	+	AD		210–1400		*53*
Caracurine V di-*N*-oxide	+		AD	2			*53*
1-Carbomethoxy-β-carboline	+						*41*
Catharanthine	+	+	AD	50			*51*
Cinchonine	+		SP			1	*56*
Cinchophylline	+		AD		16–32		*69*
Conoduramine	+	+	AD		15–400		*59–60*
Conodurine	+	+	AD		4–400		*59,60*
Cryptolepine	+						*61*
16-Decarbomethoxytetrahydrosecamine	+	−	AD				*42,43*
18,19-Dehydro-ochrolifuanine F	+	+	AD				*69*

Dehydropteleatinium	+	+	AL		50–100		*94*
Dictamnine	+		BG		10		*95*
Dihydrocinchonine	+		AL				*50*
18,19-Dihydrocinchophylline	+		AD				*69*
Dihydrocorynantheol	+	–	BG				*42,62,63*
4,5-Dimethoxycanthin-6-one	+						*41*
10,10′-Dimethoxy-*N*-methyltetrahydrousambarensine	+		AD				*69*
Diploceline	+				500–2000		*64*
Fagarine	+		BG		20		*95*
Glycozolidol	+	+	AD		200		*65*
Gramine	+	+	LD				*113*
Harmaline	+	+	PD	4			*67*
		+	SP		10 (light)		*66*
		+	SP			1	*56*
Harmalol	+	+	PD	4			*67*
Harman		+	SP		10 (light)		*66*
Harmine	+	+		<100			*68*
		+	SP		10 (light)		*66*
Harmol	+	+					*68*
3-Hydroxyconoduramine	+	+	AD		8–170		*45*
3-Hydroxyconodurine	+	+	AD		14–750		*45*
3-Hydroxyconopharyngine	+		AL		60–140		*47*
3-Hydroxyisovoacangine	+	+	AL		50–500		*45*
3′-Hydroxy-N^4-demethylervahanine B	+		BG				*44*
3′Hydroxy-N^4-demethyltabernamine	+		BG				*44*
19-Hydroxy-18,19-dihydrocinchophylline	+		AD				*69*
9-Hydroxyellipticine	+	+	AD		1–250		*48,49*
3-Hydroxy-(19*R*)-heyneanine	+		BG				*44*
5-Hydroxy-4-methoxycanthin-6-one	+						*41*

(*continued*)

TABLE VI (*Continued*)

Alkaloid	Active against Gram (+)	Active against Gram (−)	Test	Concentration tested (μg/m)	MIC (mg/ml)	ED_{50} (mg/ml)	Ref.
10′-Hydroxy-10-methoxy-*N*-methyltetrahydrousambarensine	+		AD				*69*
3′-Hydroxytabernamine	+		BG				*44*
16-Hydroxytetrahydrosecamine	+		BG				*43,43*
10-Hydroxyusambarensine	+		AD				*69*
3-Hydroxyvoacamine	+	+	BG				*45*
Ibogaine	+		AD		50		*46*
Ibogamine	+	+	AL	1	1000		*50*
Iboxygaine	+		AL	1	1000		*50*
Isoraunescine	+		AL	1	1000		*50*
Isovoacangine	+		AL	1	1000		*50*
Melicopicine	+		AD		>200		*97*
6-Methoxytecleanthine	+		AD		>200		*97*
11-Methoxytubotaiwine	+	−	AD				*42,43*
Mimosamycin	+				100		*93*
Norharmane		+	SP		10 (light)		*66*
Ochrolifuanine A	+		BG		32		*43,69*
Ochrolifuanine E	+		AF				*69*
Ochrolifuanine F	+	+	AF		32		*69*
Perivine	+	+	AD	15			*51*
Pteleatinium	+	+	AL		100–1000		*94,96*
Ptelefolonium	+	−					*42*
Renierol	+				100		*93*
Reserpine		+	AD	37			*51*
Stemmadine	+	+	SP		1–7		*70*
Strychnine	−		AD	5			*53*
	+		SP			1	*56*

Tabernaemontanine		+	AD	38			*51*
Tabernanthine	+		AL	1	1000		*50*
Tchibangensine	+		AD		64		*69*
Tecleanthine	+		AD		>200		*97*
Tetrahydroalstonine	+	+	AD	54			*51*
Tetrahydrosecamine	+	−	AD		110		*62,63*
Tetrahydrousambarensine	+		AD		32		*69*
Usambarensine	+		AD				*69*
Vindoline	+	+	AD	38			*51*
Vindolinine	+	+	AD	70			*51*
Voacamine	+	+	AD		20–400		*60*
Vobparicine	+	+	AD		50–100		*45*
Vobparicine *N*-oxide	+		BG				*45*
Woodinine	+	+	AD				*72*
Yuehchukene	+				20–25		*71*
Alkaloids derived from phenylalanine/tyrosine							
Actinodaphnine	+	+	AL		50–300		*74*
Anhydroushinsunine	+	−	AL		50		*74*
Anolobine	+	+	AL		6–200		*80,81*
Anonaine	+	+	AL		3–100		*80,81*
	+	−	AL		50		*74*
Berbamine	+	+			125–1000		*73*
Berberine	+	+	AL		1000		*50*
	+	+	AL		3–100		*89*
	+		SP			1	*56*
Berberrubine	+	−	AL		100		*90*
Bulbocapnine	+	−	AL		1000		*50*
Cassameridine	+	−	AL		25–50		*82*
Cepharanthine	+	+			8–1000		*73*
Chelerythrine	+	+	AL		6–100		*50,84,85*

(*continued*)

TABLE VI (*Continued*)

Alkaloid	Active against: Gram (+)	Active against: Gram (−)	Test	Concentration tested (μg/m)	MIC (mg/ml)	ED_{50} (mg/ml)	Ref.
Chelidonine	+	−	AL		1000		*50*
	+	+	AL		1000–10,000		*86*
	+		AL		20–50		*87*
	+	+	AL		30–500		*42*
Chelidonine *N*-oxide	+	+	AL		1000–10,000		*86*
Columbamine	+	−	AL		100		*79*
Corytuberine	−	−	AL				*80,81*
l-Curine	+	−	AL		1000		*50*
Dehatrine	+	−	AL		300		*74*
Dehydroglaucine	+	−	AL		25		*83*
Dihydroberberine	+	+	AL		1000		*50*
Fagaronine		+	SP				*88*
Funiferine	+	−	AL		100		*50*
Glaucine	+	−	AL		300		*74*
Hernandezine	+	−	AL		25–100		*75*
Isoboldine	−	−	AL				*80,81*
Isotetrandine	+	+	AL		100–200		*76*
Isotrilobine	+	+			8–500		*73*
Liriodenine	+	+	AL		1–100		*80,81*
	+		SP		0.4–3		*83*
Lysicamine	+	−	AL		12–26		*82*
Magnoflorine	−	−	AL				*78,79*
N-Desmethylthalidezine	+	−	AL		50–1000		*75*
N-Desmethylthalistyline	+	−	AL		100–1000		*75*
N-Methylactinodaphnine	+	+	AL		50–300		*74*
Nornantenine	+	+	AL		3–100		*80,81*
Nuciferine	+	−	AL		1000		*50*

O-Methyldauricine	+	−		250–1000		*73*
O-Methylthalibrine	+	−	AL	100		*77*
O-Methylthalmethine	+	−	AL	100		*75*
Obamegine	+	+	AL	50–200		*76*
Oxonantenine	+	−	AL	6–25		*82*
Oxyacanthine	+	+		62–100		*73*
Palmatine	+	+	AL	1000		*50*
Papaverine	+		SP		1	*56*
Pennsylvanine	+	−	AL	1000		*75*
Protopine	+		AL	100		*87*
	+	−	AL	300		*74*
Protothalipine	+	−	AL	1000		*79*
Sanguinarine	+	+	AL	13–100		*84*
	+		AL	1–5		*87*
	+		SP		0.01	*56*
Tetrandrine	+	+		15–1000		*73*
Thalibrine	+	−	AL	1000		*75*
Thalicarpine	+	−	AL	100–1000		*42,78*
Thalicerbine	+	+		250–1000		*73*
Thalidasine	+	+	AL	25–200		*76*
Thalidezine	+	+	AL	100		*75*
Thaliglucinone	+	+	AL	25–200		*79*
Thalistine	+	−	AL	100		*77*
Thalistyline	+	−	AL	50		*75*
Thalmelatine	+	−	AL	100		*42,78*
Thalmirabine	+	−	AL	100		*77*
Thalphenine	+	−	AL	1000		*78,79*
Thalrugosaminine	+	−	AL	50–100		*78,79*
Thalrugosidine	+	+	AL	100–200		*76*
Thalrugosine	+	+	AL	100–200		*76*
Tubocurarine	+		SP		1	*56*

(*continued*)

TABLE VI (*Continued*)

Alkaloid	Active against		Test	Concentration tested (μg/m)	MIC (mg/ml)	ED_{50} (mg/ml)	Ref.
	Gram (+)	Gram (−)					
Xylopine	+	+	AL		50–100		*74*
Steroidal alkaloids							
Conessine	+	+	AL		100–1000		*50*
Samandarone	+	+	LD				*113*
Samandarine	+	+	LD				*113*
Solacasine	+		AL		3–13		*50*
Solanidine	+	+	AL		1000		*50*
Solanocapsine	+		AL		3		*91*
	+	+	AL		100		*91*
Quinolizidine alkaloids							
Angustifoline	+	−			50 m*M*		*99*
13-Hydroxylupanine	+	−			50 m*M*		*99*
Lupanine	+	−			50 m*M*		*99*
Sparteine	+	−	SP			<0.5–10 m*M*	*98*
13-Tigloyloxylupanine	+		AD			5 m*M*	*98*
Pyrrolizidine alkaloids							
Lasicarpine	+				50		*100*
Miscellaneous alkaloids							
Antofine	+	+	BG				*115*

Benzoxazolinone (BOA)	+					*105*
Chaksine	+		AL		100	*101*
Dihydrookolasine	+		AL		128	*103*
Dihydrowisanine	+		AL		128	*103*
DIMBOA/MBOA		−				*106*
Diplamine	+	+				*111*
Ecteinascidins	+					*109*
Ficuseptine	+	+	BG			*115*
Hydroxyrutacridone epoxide	+	+	TLC		0.1–10	*95*
6-Methylspinaceamine		+	LD			*113*
Rutacridone epoxide	+	+	TLC		0.2–5	*95*
Scutlianins A–E	+			1		*110*
Spinaceamine		+	LD			*113*
Tryptanthrine	+		AL		3–6	*104*
Tuberin	+	+	SP		0.1–1	*107,108*
Ungeremine	+	+				*114*
Wisanine	+		AL		128	*102*
Xestoaminol A	+	+	AD			*112*

[a] +, active; −, no activity observed in the concentration range tested (many alkaloids were only assayed in low concentrations as microbial antibiotics); AD, agar diffusion, AL, agar dilution; BG, biogram; LD, liquid culture; MIC, minimal inhibitory concentration; PD, paper disk; SP, suspension; TLC, TLC disk test according to Wolters and Eilert (*95*). If more than one value is given, the data refer to different bacterial species tested.

derive from tryptophan (indole alkaloids) and phenylalanine/tyrosine, which may be due to the fact that these alkaloids have obtained considerable scientific attention since the discovery of many medicinally important compounds within these groups (*42,50,59,60,63,68,75–84*). Some of these alkaloids are highly antibiotic, with similar activities as fungal antibiotics, namely, cinchophylline (*69*), dictamnine (*95*), fagarine (*95*), stemmadine (*70*), yuehchukene (*71*), liriodenine (*83*), lysicamine (*82*), oxonantenine (*82*), sanguinarine (*87*), solacasine (*50,92*), rutacridone epoxide (*95*), tryptanthrine (*104*), and tuberin (*107,108*) (Table VI).

In many instances, when alkaloids are assessed for their antibacterial activity, they are often also tested for antifungal properties. Usually yeasts and *Candida* are used as test organisms (Table VII). Table VII lists 117 alkaloids with antifungal activity. Besides indole, quinoline, and isoquinoline alkaloids, the group of steroidal alkaloids shows significant activities. Especially active compounds include dictamnine (*95*), skimmianine (*95*), anolobine (*80,81*), berberine (*89,120*), cassameridine (*82*), chelerythrine (*119*), chelidonine (*120,121*), dehydroglaucine (*83*), liriodenine (*83,118*), lysicamine (*82*), sanguinarine (*119,121*), thaliglucinone (*79*), demissidine (*126,127*), solacasine (*92*), soladulcidine (*126,127*), solasodine (*26,127*)tidine (*126,127*), tomatine (*42,126*), verazine (*124*), cryptopleurine (*133*) hydroxyrutacridone epoxide (*95*), tryptanthrine (*104*), and tuberin (*107*).

Whereas the mode of action and targets of antibiotics of fungal and bacterial origin have been elucidated in many instances (see Table IV), relevant information for plant-derived compounds is scant. However, the molecular targets of some alkaloids have been determined at the general level, but not specifically for bacterial or fungal systems (Table IV) that may be responsible for the antibiotic effects observed. The following interactions of alkaloids having antimicrobial properties with molecular targets of bacterial or fungal cells are likely (compare Tables VI and VII with Tables IV and V). Protein biosynthesis in ribosomes is affected by sparteine (*56,417*), lupanine, angustifoline, 13-tigloyloxylupanine, and 13-hydroxylupanine (*56,98,99,417,421,422*). Intercalation or binding to DNA is influenced by fagaronine, dictamnine (*367*), harman alkaloids (*376,378*) [binding to DNA is light dependent (*66*)], berberine (*396–398*), chelerythrine (*400*), and sanguinarine (*400,409*); these compounds may thus inhibit important processes such as DNA replication and RNA transcription that are also vital for microorganisms. The stability of biomembranes may be disturbed by cepharanthine, tetrandrine, and steroidal alkaloids such as solamargine (*435*), solanine (*430,432,433*), and solasonine (*435*), thus leading to an uncontrolled flux of metabolites and ions into microbial cells. Inhibition of metabolically important enzymes is affected by berberine (*399*), chelerythrine (*259,401*), chelidonine (*402*), palmatine (*399*), sanguinarine (*143,259*), solacongestidine (*434*), and papaverine.

In contrast to antibiotics of microbial origin that could be classified as alkaloids from a chemical point of view in many instances, and which often interfere with the biosynthesis or maintenance of the cell wall (murein) (Table IV), such an interaction has not been described for plant-derived compounds. Since this topic has not been studied in detail it remains open whether this complex is another target for alkaloids.

We can distinguish between secondary metabolites that are already present prior to an attack or wounding, so-called constitutive compounds, and others that are induced by these processes and made *de novo*. Inducing agents, which have been termed "elicitors" by phytopathologists, can be cell wall fragments of microbes, the plant itself, or many other chemical constituents (*4,17,22–24*). The induced compounds are called "phytoalexins," which is merely a functional term, since these compounds often do not differ in structure from constitutive natural products. In another way this term is misleading, since it implies that the induced compound is only active in plant–microbe interactions, whereas in reality it often has multiple functions that include antimicrobial and antiherbivoral properties (see below).

Many of the antimicrobial alkaloids found are constitutively expressed and accumulated, that is, they are already present before an infection. Using plant cell cultures, it was observed that some cultures start to produce new secondary metabolites when challenged with bacterial or fungal cell walls, culture fluids, or other chemical factors (*4,17,22–24*). Among the compounds found to be inducible are alkaloids such as sanguinarine and hydroxyrutacridone epoxide (see Table XI). Quinolizidine alkaloids display some antimicrobial properties, besides their main role in antiherbivore defense (*503*) (see Table I). On wounding, QA production is enhanced, thus increasing the already high alkaloid concentration in the plant; in other words, the antimicrobial and herbivoral effect is further amplified (Table XI) (*2,184,503*).

The reactions leading to the induction and accumulation of phytoalexins with phenolic structures have been studied in molecular detail (*4,17,22–24*). These studies revealed that plants can detect and react rapidly to environmental problems, such as wounding or infection: Within 20 min of elicitation, mRNAs coding for enzymes that catalyze the reactions leading to the respective defense compounds are increasingly generated, leading to the accumulation of the respective enzymes and consequently the production of the secondary metabolites (*4,17,22–24*). Similar processes are likely for alkaloids, but so far the mechanisms have not been elucidated.

We assume that a substantial number of the 10,000 alkaloids have antimicrobial properties (which remain to be tested in most cases) that are directed against the ubiquitous and generalist microbes which have not

TABLE VII

ANTIFUNGAL ACTIVITY OF ALKALOIDS

Alkaloid	Active against	Test	Concentration tested (mg/ml)	MIC (μg/ml)	ED_{50} (mg/ml)	Ref.
Alkaloids derived from tryptophan						
Affinisine	Yeast	AL	1	1000		*50*
Ajmalicine	Fungi	AD	15			*51*
Apparicine	Fungi	AD	12			*51,52*
Bisnordihydrotoxiferine	Yeast	AD		270–3000		*53*
	Yeast, fungi	AL		40–100		*54*
	Phytopathogens	AL		40–100		*54*
Brevicolline	Fungi					*57*
Canthin-6-one	Fungi					*57*
Carcurine V	Yeast	AD		210–1400		*53*
Catharanthine	Fungi	AD	50			*51*
Dihydrocinchonine	Yeast	AL	1			*42,128*
Dihydropteleatinium	Yeast	AL		50–100		*94,131*
	Fungi	TLC		20–100		*95*
Gramine	Yeast, fungi	AD				*113*
	Erysiphe graminis	AL			<2 m*M*	*132*
Harmine	Yeast					*68*
Harmol	Yeast					*68*
Ibogamine	Yeast	AL	1	1000		*50*
Isatin (2,3-indolinedione)	*Lagenidium*					*117*
Reserpine	Fungi	AD	37			*51*
Tetrahydroalstonine	Fungi	AD	54			*51*
Vindoline	Fungi	AD	38			*51*
Alkaloids derived from phenylalanine/tyrosine						
Actinodaphnine	*Candida*	AL		250–1000		*74*
Anhydroushinsunine	*Candida*	AL		125–1000		*74*
Anolobine	Yeast	AL		6–200		*80,81*

Anonaine	Yeast	AL	3–100	*80,81*
	Candida	AL	62–259	*74*
Berberine	Yeast	AL	1000	*50*
	Yeast, fungi	AL	3–100	*89*
	Yeast, fungi	AL	15–500	*120*
Boldine	*Candida*	AL	250	*74*
Bulbocapnine	Yeast	AL	1000	*50*
Cassameridine	Yeast, fungi	AL	25–50	*82*
Chelerythrine	Yeast	AL	6–100	*50*
	Yeast	SP	10	*119*
Chelidonine	Yeast, fungi	AL	1000–10,000	*42,50,86*
	Yeast, fungi	AL	15–125	*120*
	Fungi	TLC	25	*121*
Chelidonine *N*-oxide	Yeast, fungi	AL	1000–10,000	*86*
Coclaurine	*Candida*	AL	1000	*74*
Columbamine	*Candida*	AL	100	*79*
Dehatrine	*Candida*	AL	1000	*74*
Dehydroglaucine	Yeast	AL	25–50	*83*
N-Desmethylthalidezine	Yeast	AL	1000	*75*
Dihydroberberine	Yeast	AL	1000	*50*
	Fungi	CT	25	*121*
Glaucine	*Candida*	AL	1000	*74*
Hernandezine	*Candida*	AL	50	*75*
Jatrorrhizine	Yeast	CT	250	*122,123*
Laudanosine	*Candida*	AL	500–1000	*74*
Laurotanine	*Candida*	AL	1000	*74*
Liriodenine	Yeast, fungi	AL	6–100	*80,81*
	Yeast, fungi	AL	6	*83*
	Candida	AL	3	*118*
Lysicamine	Yeast, fungi	AL	12–26	*82*
N-Methylactinodaphnine	*Candida*	AL	125–1000	*74*

(*continued*)

TABLE VII (*Continued*)

Alkaloid	Active against	Test	Concentration tested (mg/ml)	MIC (μg/ml)	ED_{50} (mg/ml)	Ref.
O-Methylbulbocapnine	*Candida*	AL		500–1000		*74*
O-Methylthalibrine	*Candida*	AL		500		*77*
Nornantenine	Yeast	AL		3–100		*80,81*
Oxonantenine	Yeast, fungi	AL		6–25		*82*
Oxyacanthine	Yeast	AL		1000		*50*
Palmatine	Yeast	AL		1000		*50*
	Fungi	CT		250		*122,123*
Sanguinarine	Yeast	AL		12–100		*50*
	Yeast	SP		10		*119*
	Fungi	CT		5–25		*121*
	Yeast, fungi	AL		2–250		*120*
Thalibrine	*Candida*	AL		1000		*42,78*
Thalicarpine	*Candida*	AL		1000		*42,78*
Thalidezine	Yeast	AL		100		*75*
Thaliglucinone	*Candida*	AL		50		*79*
Thalphenine	*Candida*	AL		1000		*42,78*
Xylopine	*Candida*	AL		250		*74*
Steroidal alkaloids						
Cevadine	Fungi	CT	1			*125*
Conessine	Fungi	CT		30–250		*126,127*
	Yeast	AL		100–1000		*128*
Demissidine	Fungi	CT		5		*126,127*
	Fungi	TLC		4–20		*126,127*
Isorubijervine	Fungi	CT		150		*125*
	Yeast, fungi			72–200		*129,130*
Jervine	Fungi	CT	0.1			*125*
	Yeast, fungi			9–120		*129,130*

Protoveratrine A	Fungi	CT	1		*125*
Protoveratrine B	Fungi	CT	1		*125*
Pseudojervine	Fungi	CT	1		*125*
	Yeast, fungi			19–54	*129,130*
Rubijervine	Fungi	CT		150	*125*
Samandarone	Yeast, fungi			0.34 m*M*	*113,529*
Samandarine	Yeast, fungi				*113,529*
Samandaridine	Yeast, fungi				*113,529*
Solacasine	Yeast	AL		3–13	*121*
Solacongestidine	Yeast, fungi	AL		0.8–1	*124*
Soladulcidine	Fungi	CT		15	*126,127*
	Fungi	TLC		20	*126*
Soladulidininetatraosid	Fungi	CT		10–50	*126,127*
Solafloridine	Yeast, fungi	AL		6–100	*124*
Solamargine	Fungi	CT		40	*126,127*
	Fungi	TLC		>80	*42*
	Yeast	AL		1000	*128*
Solanidine	Fungi	CT		5	*126,127*
	Fungi	TLC		20–40	*121*
	Yeast	AL		1000	*128*
Solanine	Fungi	CT		40	*126,127*
Solanocapsine	Fungi	TLC		10	*121*
	Yeast	AL		100	*121*
Solasodine	Fungi	CT		15	*126,127*
	Fungi	TLC		20	*121*
	Yeast	AL		>100	*124*
Solasonine	Fungi	CT		40	*126,127*
Tomatidenol	Fungi	CT		1–40	*121,126,127*
Tomatidine	Fungi	CT		2–22	*126,127*
	Fungi	TLC		15	*126*
Tomatillidine	Yeast, fungi	AL		>100	*124*

(*continued*)

TABLE VII (*Continued*)

Alkaloid	Active against	Test	Concentration tested (mg/ml)	MIC (μg/ml)	ED_{50} (mg/ml)	Ref.
Tomatine	Fungi	CT		2–40		*126,127*
	Fungi	TLC		5		*42,126*
Veratramine	Yeast, fungi			72–200		*129,130*
Veratridine	Fungi	CT	1			*125*
Veratrobasine	Yeast, fungi			72–200		*129,130*
Verazine	Yeast, fungi	AL		3–12		*124*
Quinolizidine alkaloids						
Lupanine	*Erysiphe graminis*	AL			2 m*M*	*132*
Sparteine	*Erysiphe graminis*	AL			<2 m*M*	*132*
	Fungi	AL			5–50 m*M*	*98*
13-Tigloyloxylupanine	*Erysiphe graminis*	AL				*132*
Miscellaneous alkaloids						
Antofine	Fungi					*113*
Benzoxazolinone (BOA)	Fungi					*105*
Cryptopleurine	*Candida*, fungi	AL		0.1		*133*
Dictamnine	Fungi	TLC		10–100		*95*
6,6′-Dihydroxythiobinupharidine	Fungi	AL		0.1		*134*
DIMBOA/MBOA	Phytopathogenic fungi					*106*
3,4-Dimethoxy-(piperid-2-yl)-acetophenone	*Candida*	AL		3		*133*

Eupolauridine	*Candida*			1.5	*135*
Ficuseptine	Fungi				*113*
Hydroxyrutacridone epoxide	Yeast, fungi	TLC		0.1–10	*95*
Julandine	*Candida*	AL		12.5	*133*
Lasiocarpine	*Candida/ Aspergillus*			50	*100*
Melicopicine	*Cladosporium*	TLC			*97*
6-Methoxytecleanthine	*Cladosporium*	TLC			*97*
Onychine	*Candida*			3.1	*135*
Papuamine	*Trichophyton*			10	*136*
Phidolopine	*Helmithosporium, Rhizoctonia*			70	*137*
Pteleatinium	Yeast	AL		100–1000	*94,131*
Rutacridone epoxide	Yeast, fungi	TLC		0.2–5	*95*
Scutianins A–E	*Pythium*		1		*110*
Skimmianine	Fungi	TLC		>100	*95*
Stemmadine	*Candida*	SP	37		*70*
Supinine	*Candida*			50	*100*
Tecleanthine	*Cladosporium*	TLC			*97*
Tryptanthrine	Yeast	AL		3–6	*104*
Tuberin	*Saccharomyces*			0.1	*107*
Xestoaminol A	*Candida, Trichophyton*				*137*

[a] CT, Channel test according to Wolters (116); other abbreviations are as in Table VI. If a range is given, the first value gives a 10% inhibition, the second value a 100% inhibition.

specialized on a particular host plant. However, alkaloid production does not necessarily have to be involved with antimicrobial defense. For example, *Phytophthora* or *Fusarium* will attack alkaloid-rich plants of *Nicotiana, Solanum esculentum,* and *S. tuberosum. Cladosporium* and *Fusarium* can develop in nutrient-containing media enriched with alkaloids, and *Aspergillus niger* can utilize alkaloids as a nitrogen source (*506*).

In addition, most plant species are known to be parasitized or infected by at least a few specialized bacteria or fungi which form close, often symbiotic, associations. In these circumstances an antimicrobial effect expected from the secondary metabolites present in the plant can often no longer be observed. We suggest that these specialists have adapted to the chemistry of their host plants. Mechanisms may include inhibition of biosynthesis of the respective compounds, degradation of the products, or alteration of the target sites, which are then no longer sensitive toward a given compound (so-called target site modification). These mechanisms need to be established for most of the microbial specialists living on alkaloid-producing plants. Some associations between plants and fungi are symbiotic in nature, such as *Rhizobia* in root nodules of legumes or microrhizal fungi in many species. In lupines, nitrogen-fixing *Rhizobia* are present both in alkaloid-rich and alkaloid-free plants. They must therefore be able to tolerate the alkaloids, which are also present in the root. Alkaloid production in lupines is more or less unaffected whether or not the plants harbor *Rhizobia* (*185,506*).

An ecologically important symbiosis between plants and fungi can be observed in fungal species that produce ergot alkaloids. Graminaceous species that are infected by ergot suffer much less from herbivory because of the strong antiherbivoral alkaloids produced by the fungi (*4*). A similar relationship may occur for other fungal species of plants, many of which produce secondary metabolites possessing animal toxicity.

From the pharmaceutical point of view, few alkaloids are interesting as antibiotics, because many are highly toxic to vertebrates (Tables II and III). Since many alkaloids are antibacterial and antifungal (Tables VI and VII) and are present in plants at relatively high concentrations (Section III,A), it seems likely that from an ecological perspective alkaloids, besides their prominant role in antiherbivore strategies, may play an important role also in the defense against microbial infections. It should be recalled that even alkaloid-producing plants synthesize antimicrobial proteins, such as chitinase and lysozyme, and other antimicrobial secondary products, such as simple phenolics, flavonoids, anthocyanins, saponins, and terpenes (*2–4,7*). A cooperative, or even synergistic, process could thus be operating.

C. Antiviral Properties

Plants, like animals, are hosts for a substantial number of viruses, which are often transmitted by sucking insects such as aphids and bugs (Heteroptera). Resistance to viral infection can be achieved either by biochemical mechanisms that inhibit viral development and multiplication or by warding off vectors such as aphids in the first place.

The assessment of antiviral activity is relatively difficult. As a result, only a few investigators have studied the influence of alkaloids on virus multiplication. Nevertheless, at least 45 alkaloids have been reported with antiviral properties (Table VIII). Only sparteine (*527*) and cinchonidine (*142*) have been tested for antiviral activities against a plant virus, the potato X virus. All other evidence for antiviral activities (Table VIII) of alkaloids comes from experiments with animal viruses. Because viral life strategies are related in plants and animals, we suggest that a wider number of plant viruses may be controlled by alkaloids in Nature than the limited data imply.

Viral multiplication can be controlled at the level of replication, transcription, protein biosynthesis, and posttranslational protein modification. The number of molecular targets is thus quite restricted for antiviral activities (compare Tables IV and VIII). The processing of DNA and RNA is extremely important for viruses, and it is not surprising that this area (intercalation in DNA, binding to DNA, inhibition of RNA and DNA polymerases) is probably one of the potential targets of alkaloids, for example, camptothecine (*365,366*), quinine, β-carboline alkaloids (*138*), and acridone alkaloids (*145*). Other alkaloids could inhibit protein biosynthesis or posttranslational protein modifications. Examples include polyhydroxy alkaloids (*150,212,410–414*), cryptopleurine (*404,444*), haemanthamine (*390*), hippeastrine (*148*), narciclasine (*451*), pretazettine (*390*), sparteine and other QAs, and pseudolycorine (*390*). Because retroviruses rely on reverse transcriptase, inhibition of this enzyme by alkaloids would have a dramatic effect. However, plant viruses are not retroviruses, and the significance of the anti-reverse transcriptase effects of the alkaloids listed in Table VIII are difficult to interpret at present. Polyhydroxy alkaloids, such as swainsonine, can block the action of endoplasmic reticulum- and Golgi-localized glucosidases and mannosidases, which are important for the posttranslational trimming of viral envelope proteins.

Because alkaloids often deter the feeding of insects, such as aphids and bugs (Table I), viral infection rates may be reduced in alkaloid-rich plants. Such a correlation exists for alkaloid-rich lupines (so-called bitter

TABLE VIII

ANTIVIRAL ACTIVITY OF ALKALOIDS

Alkaloid	Activity	ED_{50} (μg/ml)	Ref.
Alkaloids derived from tryptophan			
Apparicine	Anti-polio III activity	—	*141*
Camptothecine	Inhibition of herpes and other virus	—	*140*
Cinchonidine	Inhibition of potato X virus	—	*142*
Dimethoxy-1-vinyl-β-carboline	Inhibition of herpes simplex virus	—	*138*
Eudistomins C, E, K, L (tunicates)	Inhibition of herpes simplex virus	—	*109*
Harman	Inhibition of herpes simplex virus	—	*138*
Harmine	Inhibition of murine cytomegalovirus, Sindbis virus	—	*139*
7-Methoxy-1-methyl-β-carboline	Inhibition of herpes simplex virus	—	*138*
Norharman	Inhibition of herpes simplex virus	—	*138*
Alkaloids derived from phenylalanine/tyrosine			
Fagaronine	Inhibition of reverse transcriptase of oncorna virus	—	*143*
Acridone alkaloids			
Acronycine	Inhibition of herpes simplex virus	3.3	*145*
Atalaphillidine	Inhibition of herpes simplex virus	0.7	*145*
Atalaphillinine	Inhibition of herpes simplex virus	0.8	*145*
Citpressine I	Inhibition of herpes simplex virus	0.6	*145*
Citracridone I	Inhibition of herpes simplex virus	1.3	*145*
Citrusinine I	Inhibition of herpes simplex virus	0.7	*145*
Dercitine (sponge)	Inhibition of herpes simplex virus, murine corona virus	1–5	*144*
Dimethoxyacronycine	Inhibition of herpes simplex virus	6.5	*145*
Glycocitrine I	Inhibition of herpes simplex virus	5	*145*
Glyfoline	Inhibition of herpes simplex virus	>20	*145*
Grandisine	Inhibition of herpes simplex virus	10	*145*

5-Hydroxy-*N*-methylseverifoline	Inhibition of herpes simplex virus	2.0	*145*
5-Hydroxynoracronycine	Inhibition of herpes simplex virus	5	*145*
5-Methoxyacronycine	Inhibition of herpes simplex virus	5.5	*145*
N-Methylatalaphilline	Inhibition of herpes simplex virus	8.4	*145*
Miscellaneous alkaloids			
Abikoviromycin	Antiviral activities	—	*149*
Ageliferin	Inhibition of herpes simplex virus	—	*109*
Crinamine	Inhibition of Rauscher virus NIH/3T3 cells	MAD[a] 0.2 μg/ml	*147*
Cryptopleurine	Inhibition of herpes simplex virus	—	*141*
Sceptrin	Inhibition of herpes simplex virus	—	*109*
Didemnin	Inhibition of herpes simplex virus	—	*109*
Haemanthamine	Inhibition to Rauscher virus NIH/3T3 cells	MAD 0.2 μg/ml	*147*
Hippeastrine	Inhibition of herpes simplex virus	—	*148*
6-Hydroxycrinamine	Inhibition to Rauscher virus NIH/3T3 cells	MAD 0.2 μg/ml	*147*
Lycorine	Inhibition to Rauscher virus NIH/3T3 cells	MAD 0.2 μg/ml	*147*
	Inhibition of herpes simplex virus	—	*148*
Maytansine	Inhibition of murine sarcoma virus	—	*146*
Narciclasine	Inhibition to Rauscher virus NIH/3T3 cells	MAD 0.005 μg/ml	*147*
Oxysceptrine	Inhibition of herpes simplex virus	—	*109*
Precriwelline	Inhibition to Rauscher virus NIH/3T3 cells	MAD 0.05 μg/ml	*147*
Pretazettine	Inhibition to Rauscher virus NIH/3T3 cells	—	*147*
	Inhibition of herpes simplex virus	—	*148*
Pseudolycorine	Inhibition to Rauscher virus NIH/3T3 cells	MAD 1.0 μg/ml	*147*
	Inhibition of herpes simplex virus	—	*148*
Sparteine	Inhibition of potato x virus	—	*150*
Polyhydroxy alkaloids			
Castanospermine	Inhibition of cytomegalovirus, retroviruses	0.8 m*M*	*150*
Deoxynorjirimycin	Inhibition of cytomegalovirus, retroviruses	1.0 m*M*	*150*
Dihydroxymethyl-dihydroxypyrrolidine	Inhibition of cytomegalovirus, retroviruses	1.8 m*M*	*150*

[a] MAD, Minimal active dose.

lupines) and low-alkaloid varieties (the so-called sweet lupines) (see Table XII).

D. Allelopathic Properties

Plants often compete with other plants, of either the same or different species, for space, light, water, and nutrients. This phenomenon can be intuitively understood when the flora of deserts or semideserts is analyzed, where resources are limited and thus competition intense (*4,17,498–500*). A number of biological mechanisms have been described, such as temporal spacing of the vegetation period in which some species flower at an earlier season, when others are still dormant or ungerminated.

It was observed by Molisch in 1937 (*497*) that plants can also influence each other by their constituent natural products, and he coined the term "allelopathy" for this process. Secondary products are often excreted by the root or rhizosphere to the surrounding soil, or they are leached from the surface of intact leaves or from decaying dead leaves by rain (*4,17*). Both processes will increase the concentration of allelochemicals in the soil surrounding a plant, where the germination of a potential competitor may occur. Allelopathy, namely, the inhibition of germination or of the growth of a seedling or plant by natural products, is well documented at the level of controlled *in vitro* experiments (*4,17,19,497–500*), but how it operates in ecosystems is still often a matter of controversy. It is argued, for example, that soil contains a wide variety of microorganisms which can degrade most organic compounds. Thus allelochemicals might never reach concentrations high enough to be allelopathic.

Allelopathic natural products have been recorded in all classes of secondary metabolites. Few research groups have studied the effect of alkaloids in this context, but at least 50 alkaloids have been reported with allelopathic properties (Table IX). As can be seen from Table IX, allelopathic activities can be found within nearly all structural types of alkaloids. At higher alkaloid concentrations, a marked reduction in the germination rate can be recorded regularly. More sensitive, however, is the growth of the radicle and hypocotyl. They respond to alkaloids at a much lower level, and usually a reduction in growth can be observed but sometimes also the opposite, either of which reduces the fitness of a seedling. In species which produce the compounds, the inhibitory effects can be absent, as was reported for quinolizidine alkaloids in lupines and colchicine in *Colchicum autumnale* (*503,506*). It is likely that autotoxicity is prevented either by a special modification of cellular target sites or by other mechanisms.

TABLE IX

ALLELOPATHIC ACTIVITY OF ALKALOIDS

Alkaloid	Activity	ED_{50}	Ref.
Alkaloids derived from tryptophan			
Quinine	Toxic to *Cinchona* cells	—	*244*
	Toxic for *Lemna*	0.04%	*56*
Cinchonidine	Toxic to *Cinchona* cells	—	*244*
	Toxic for *Lemna*	0.04%	*56*
Cinchonine	Toxic to *Cinchona* cells	—	*244*
	Reduction of radicle length in *Lepidium, Lactuca*	0.01%	*56*
Ergometrine	Reduction of radicle length in *Lepidium*	0.1%	*56*
Ergotamine	Reduction of radicle length in *Lepidium*	0.1%	*56*
Gramine	Reduction of radicle length in barley	—	*239*
	Growth inhibition of *Stellaria, Capsella, Nicotiana*	—	*240*
	Reduction of radicle length in *Lepidium, Lactuca*	0.1%	*56*
Harmaline	Reduction of radicle length in *Lepidium*	0.01%	*56*
	Toxic for *Lemna*	0.04%	*56*
Hordenine	Reduction of radicle length in barley	—	*239*
5-Hydroxytryptophan	Growth inhibition	—	*238*
Physostigmine	Toxic for *Lemna*	0.4%	*56*
	Inhibition of germination	—	*241*
Quinidine	Toxic to *Cinchona* cells	—	*244*
	Reduction of radicle length in *Lepidium, Lactuca*	0.1–0.01%	*56*
	Toxic for *Lemna*	0.4%	*56*
Strychnine	Reduction of radicle length in *Lepidium*	0.1%	*56*
	Toxic for *Lemna*	0.4%	*56*
Yohimbine	Toxic for *Lemna*	0.4%	*56*
Alkaloids derived from phenylalanine/tyrosine			
Berberine	Reduction of radicle length in *Lepidium, Lactuca*	0.01%	*56*
	Growth inhibition in plant cell cultures	—	*243*

(*continued*)

TABLE IX (*Continued*)

Alkaloid	Activity	ED_{50}	Ref.
Boldine	Toxic for *Lemna*	0.04%	*56*
Chelidonine	Reduction of radicle length in *Lepidium*	0.1%	*56*
Colchicine	Reduction of radicle length in *Lepidium*	0.01%	*56*
Emetine	Toxic for *Lemna*	0.4%	*56*
Ephedrine	Reduction of radicle length in *Lepidium*	0.1%	*56*
Morphine	Reduction of root growth, induction of polyploidy in *Allium*	—	*242*
Narcotine	Inhibition of germination	—	*241*
Papaverine	Reduction of root growth, induction of polyploidy in *Allium*	—	*242*
Salsoline	Reduction of radicle length in *Lepidium*	0.01%	*56*
Sanguinarine	Reduction of radicle length in *Lepidium, Lactuca*	0.1–0.01%	*56*
	Toxic for *Lemna*	0.4%	*56*
Tropane alkaloids			
Cocaine	Inhibition of germination	—	*241*
Hyoscyamine	Inhibition of germination, radicle growth in *Linum*	—	*245*
	Toxic for *Lemna*	0.4%	*56*
	Inhibition of germination	—	*241*
Scopolamine	Inhibition of germination, radicle growth in *Linum*, wheat	—	*245,246*
	Reduction of radicle growth in *Lactuca*	0.01%	*56*
	Inhibition of germination	—	*241*
Quinolizidine alkaloids			
Cytisine	Reduction of radicle length in *Lepidium*	0.1%	*56*
	Inhibition of seed germination in *Lactuca*	6 m*M*	*56,247*
Lupanine	Inhibition of seed germination in *Lactuca*	<10 m*M*	*247*
Sparteine	Reduction of radicle length in *Lepidium, Lactuca*	0.01–0.1%	*56*
	Inhibition of seed germination in *Lactuca*	—	*56,247*
	Inhibition of radicle growth in *Raphanus*	0.01%	*185*
	Inhibition of radicle growth in *Sinapis*	<1%	*185*
13-Tigloyloxylupanine	Inhibition of seed germination in *Lactuca*	<6 m*M*	*247*

Miscellaneous alkaloids			
Aconitine	Reduction of radicle growth in *Lepidium*	0.1%	*56*
Balfourodinium	Reduction of seedlings growth in Poaceae	0.1 m*M*	*256*
	Reduction of cell growth in topinambour	40 μM	*256*
Caffeine	Autotoxicity in coffee seedlings	—	*249*
	Growth inhibition of lettuce seedlings and various species	—	*249,250*
	Reduction of radicle length in *Lepidium*	0.1%	*56*
Castanospermine	Inhibition of root length elongation	—	*253*
Coniine	Toxic for *Lemna*	0.04%	*56*
Delcosine	Reduction of cambial growth, gibberellic acid (GA) antagonism	—	*249,252*
Delsoline	Reduction of cambial growth, GA antagonism	—	*249,252*
DIMBOA and other hydroxamic acids	Inhibition of germination and seedling growth in *Abutilon*, *Lepidium*, and other plants	—	*106*
	Inhibition of *Avena fatua* growth		*255*
Lobeline	Reduction of radicle length in *Lepidium*	0.1%	*56*
	Toxic for *Lemna*	0.04%	*56*
Mimosine	Allelopathic	—	*248*
Nicotine	Reduction of radicle length in *Lepidium*	0.1%	*56*
	Toxic for *Lemna*	0.4%	*56*
	Toxic to *Trifolium*	—	*254*
8-Oxyquinoline	Reduction of radicle length in *Lepidium*	0.01%	*56*
Paraxanthine	Growth inhibition of lettuce seedlings	—	*249*
Piperine	Reduction of radicle length in *Lepidium*	0.01%	*56*
Ptelefolonium	Reduction of seedling growth in Poaceae	10 μM	*256*
	Reduction of seedling growth in *Solanum esculentum*	—	*256*
	Reduction of seedling growth in topinambour, vigne-vierge	1 μM	*256*
Theobromine	Growth inhibition of lettuce seedlings	—	*249*
Theophylline	Growth inhibition of lettuce seedlings	—	*249*
	Arrest of cell cycle in *Haplopappus* roots	—	*251*
Trigonelline	Toxic to *Trifolium*	—	*254*
α-Tripiperideine	Toxic for *Lemna*	0.4%	*56*

The mechanisms of alkaloid toxicity toward other plants have not been elucidated yet, but it is likely that the following targets are involved: DNA binding or intercalation [e.g., quinine and other quinoline alkaloids (*381*), harman alkaloids (*56,166,378*), berberine (*396–398*), sanguinarine (*400,409*) and *Veratrum* alkaloids]; inhibition of protein biosynthesis [e.g., emetine (*404*) and quinolizidine alkaloids (*56,99,416–418,422*)]; inhibition of microtubules [e.g., colchicine (*376,441,442*)]; inhibition of metabolically important enzymes [e.g., papaverine (*297,406*), colchicine (*376,441,442*), chelidonine (*402*), castanospermine (*253*), caffeine (*202,376*), and DIMBOA (*106,446–448*)]; uncoupling of electron chains [e.g., gramine (*374*), sanguinarine (*143,407*), and DIMBOA (*106,445*)]; and interference with growth factors [e.g., delcosine (*249,252*), delsoline (*249, 252*), DIMBOA (*106*), nicotine, and trigonelline (*456,457*)] (compare Tables IV and IX).

The inhibitory action of quinolizidine alkaloids should be explained in this context (*184,503*). They are very abundant in lupine seeds (up to 3–8% dry weight). During germination, 13-hydroxylupanine is converted to ester alkaloids, such as 13-tigloyloxylupanine. The latter compound is predominantly excreted via the roots of young seedlings and in germination assays proved to be the most allelopathic QA. These alkaloids influence only heterologous systems, not the germination of lupine seeds themselves. When lupine and *Lepidium* seeds were grown together in the same pot, growth of the *Lepidium* seedlings was much reduced and inhibited, indicating that QAs may also be relevant in the ecological context (*184*).

Although the number of alkaloids with known allelopathic properties is not large, owing to the limited number of studies conducted, it is clear from Table IX that alkaloids can be toxic to plants, probably by interfering with basic metabolic or molecular processes.

III. Raison d'Être of Alkaloids

Although comparably few alkaloids have been studied for their biological activities in detail, and considering that our data collection (Tables I–IX) is far from complete, we can safely state that alkaloids have potent deterrent or poisonous properties in herbivorous animals, and also affect bacteria, fungi, viruses, and plants. The next question will be whether all the adverse activities of alkaloids, which are often assayed in *in vitro* systems only, are meaningful in Nature.

A. Concentrations in Plants and Allelochemical Activities

Because most of the allelochemical activities are dose dependent (others may be synergistic, additive, etc.), the question is whether the amounts of alkaloids produced and stored in plants are high enough to be ecologically meaningful. It is difficult, and also dangerous, to make a general statement concerning alkaloid levels in plants. We must remember that alkaloid composition and levels are often tissue or organ specific (*4,25,38*). They may vary during the day [a diurnal cycle has been observed for QAs and tropane alkaloids (*185,503,506*)] or during the vegetation period (*39, 505,506*). Furthermore, as in all biological systems, there are differences at the level of individual plants and between populations and subspecies. Unfortunately, many phytochemical reports do not contain any quantitative information, or these data are given for the whole plant without realizing the above-mentioned variables. In addition, concentrations are usually given on a dry weight basis, which is appropriate in the chemical or pharmaceutical context. However, herbivores or pathogens do not feed on the dry plant in general, but on the "wet" fresh material. In the context of chemical ecology we urgently need data on a fresh weight basis. As an approximation, in this chapter we use a conversion factor of 10 to convert dry weight to fresh weight data if only the dry weight data are available.

Summarizing the relevant phytochemical literature, we find that alkaloid levels are between 0.1 and 15% (dry weight), which is equivalent to 0.01–1.5% fresh weight, or 0.1–15 mg/g fresh weight. For plants containing quinolizidine alkaloids, actual alkaloid contents are given for a number organs or parts (Table X), which fall in the range deduced before. We have evaluated the situation for quinolizidine alkaloids and found that the actual concentrations of alkaloids in the plant are usually much higher than the concentrations needed to inhibit, deter, or poison a microorganism or herbivore (*2,184,503,527*). This means that plants obviously play safe and have stored more defense chemicals than actually needed. If we look at the ED_{50} and LD_{50} values given in Tables I through IX, it is likely that the situation is similar for other alkaloid-producing plants, but these correlations need to be experimentally established in most instances.

It seems trivial that plants not only synthesize but also store their secondary products, which makes sense only in view of their ecological functions as defense compounds, since they can fulfil these functions only if the amounts stored are appropriate. Achieving and maintaining the high levels of a defense compound are very demanding from the point of view of physiology and biochemistry. Most allelochemicals would probably

TABLE X
ORGAN-SPECIFIC CONCENTRATIONS OF QUINOLIZIDINE ALKALOIDS IN SELECTED LEGUME SPECIES

Species	Organ tissue	Total alkaloids (per g fresh weight)	Ref.
Cytisus scoparius	Stem epidermis	46 mg/g; 200 m*M*	*486*
	Shoots	2 mg	*487,488*
	Leaves	0.2–1 mg	*487,488*
	Seeds	2 mg dry wt	*487,488*
	Roots	0.03 mg	*487,488*
Laburnum anagyroides	Leaves	0.3 mg	*184,487,492*
	Twigs		
	Bark	11.1 mg	*184,487,492*
	Wood	0.5 mg	*184,487,492*
	Flower	0.4 mg	*184,487,492*
	Fruit	0.5 mg	*184,487,492*
	Seed	10–30 mg dry wt	*184,487,492*
	Endosperm	21 mg	*492*
	Testa	2 mg	*492*
Lupinus albus	Stem epidermis	6.3 mg	*489*
	Phloem sap	0.5–1.2 mg/ml	*491*
	Leaves	2.8 mg	*184,487,490,491*
	Stem	0.7 mg	*184,487,490,491*
	Flower	4.1 mg	*184,487,490,491*
	Fruit	3.1 mg	*184,487,490,491*
	Seed	43.0 mg dry wt	*184,487,490,491*
	Roots	0.5 mg	*184,487,490,491*
L. angustifolius	Phloem sap	0.8 mg/ml	*461*
	Xylem sap	0.05 mg/ml	*461*
L. consentinii	Phloem sap	5 mg/ml	*461*
	Xylem	0.05 mg/ml	*461*
L. luteus	Stem epidermis	0.6 mg	*489*
L. mutabilis	Stem epidermis	5.3 mg	*489*
L. polyphyllus	Petiole epidermis	1.7–10 mg	*486,487,489*
	Stem epidermis	6.3 mg	*489*
	Leaves	1–4 mg	*184,487,490*
	Stems	1–2 mg	*184,487,490*
	Flower		
	Pollen	1.8 mg	*184,487,490*
	Carpels	1.3 mg	*184,487,490*
	Petals	0.4 mg	*184,487,490*
	Fruits	1.6 mg	*184,487,490*
	Seeds	30–40 mg dry wt	*184,487,490*
	Roots	0.2 mg	*184,487,490*

interfere with the metabolism of the producing plant if they would accumulate in the compartments where they are made (*25*). Whereas biosynthesis takes place in the cytoplasm, or in vesicles (berberine) or organelles such as chloroplasts (QAs, coniine), the site of accumulation of water-soluble alkaloids is the central vacuole, and that of lipophilic compounds includes latex, resin ducts, or glandular hairs (e.g., nicotine) (*4,25*).

In this context it should be recalled that many alkaloids are charged molecules at cellular pH and do not diffuse across biomembranes easily. During recent years, evidence has been obtained that at least some alkaloids pass the tonoplast with the aid of a carrier system. The next problem is determining how the uphill transport, that is, the accumulation against a concentration gradient, is achieved. Proton–alkaloid antiport mechanisms and ion trap and chemical trap mechanisms have been postulated and partially proved experimentally (*503,510,512*). Thus, the sequestration of high amounts of alkaloids in the vacuole is a complex and energy-requiring task, which would certainly have been lost during evolution were it not important for fitness.

As a rule of thumb, we can assume that all parts of an alkaloidal plant contain alkaloids, although the site of synthesis is often restricted to a particular organ, such as the roots or leaves. Translocation via the phloem, xylem, or apoplastically must have therefore occurred. Phloem transport has been demonstrated for quinolizidine, pyrrolizidine, and indolizidine alkaloids, and xylem transport for nicotine and tropane alkaloids (*36,39,511*).

B. Presence of Alkaloids at the Right Site and Right Time

If the plant relies on alkaloids as a defense compound, these molecules have to be present at the right place and at the right time. Alkaloids are often stored in specific cell layers, which can differ from the site of biosynthesis (*25,38,39*). In lupines, but also in other species (*486,489*), alkaloids are preferentially accumulated in epidermal and subepidermal cell layers, reaching local concentrations between 20 and 200 m*M* (Table X), which seems advantageous from the point of view of chemical ecology, since a pathogen or small herbivore encounters a high alkaloid barrier when trying to invade a lupine. The accumulation of many alkaloids in the root or stem bark, such as berberine, cinchonine, and quinine, can be interpreted in a similar way.

A number of plants produce laticifers filled with latex. For example, isoquinoline alkaloids in the family Papaveraceae are abundant in the latex (*39*), where they are sequestered in many small latex vesicles. In latex vesicles of *Chelidonium majus* the concentration of protoberberine and

benzophenanthridine alkaloids can be in the range of 0.6–1.2 *M*, which is achieved by their complexation with equal amounts of chelidonic acid (*512*). If a herbivore wounds such a plant, the latex spills out immediately. Besides gluing the mandibles of an insect, the high concentration of deterrent and toxic alkaloids will usually do the rest, and, indeed, *Chelidonium* plants are hardly attacked by herbivores. In addition, as these alkaloids are also highly antimicrobial (Table IV), the site of wounding is quickly sealed and impregnated with natural antibiotics. Other well-known plants that have biologically active alkaloids in their latex belong to the families Papaveraceae (genera *Papaver, Macleya*, and *Sanguinaria*) and Campanulaceae (genus *Lobelia*) (*39*).

It is intuitively plausible that a valuable plant organ must be more protected than others. Alkaloid levels are usually highest during the time of flowering and fruit/seed formation. In annual species actively growing young tissue, leaves, flowers, and seeds are often alkaloid-rich, whereas in perennial ones, like shrubs and trees, we find alkaloid-rich stem and root barks in addition. All these plant parts and organs have in common that they are important for the actual fitness or for the reproduction and thus the long-term survival of the species. Spiny species, which invest in mechanical defense, accumulate fewer alkaloids than soft-bodied ones (*15*); examples are isoquinoline alkaloids in cacti or QAs in legumes (*184*). If a plant produces few and large seeds, their alkaloid levels tend to be higher than in species with many and small seeds (*15,184*); thus, a plant with few and big seeds is generally a rich source of alkaloids, which makes sense in view of the defense hypothesis.

These few examples show that accumulation and storage of alkaloids have been optimized in such a way that they are present at strategically important sites where they can ward off an intruder at the first instance of attack. Thus, specialized locations must be regarded as adaptive.

Alkaloid concentrations can fluctuate during the vegetation period, or even during a day (*36,506*), but in biochemical terms their biosynthesis and accumulation are constitutive processes. This ensures that a certain level of defensive compounds is present at any time. Furthermore, continuous turnover is a common theme for molecules of the cells whose integrity is important, such as proteins, nucleic acids, and signal molecules. The same seems to be true for a defense compound. An alkaloid which mimics a neurotransmitter, such as hyoscyamine, nicotine, or sparteine, could be oxidized or hydrolyzed in the cell by chance, and thus would be automatically inactivated. Only by replacing these molecules continuously can the presence of the active compounds be guaranteed. For example, it was suggested that nicotine has a half-life of 24 hr in *Nicotiana* plants, and that more than 10% of the CO_2 fixed passes through this alkaloid (*505*).

In other groups of natural products it was possible to show that plants can react to infection by microbes or to wounding by herbivores by inducing the production of new defense compounds. These compounds are termed "phytoalexins" in phytopathology (*22-24*). Classic examples of phytoalexins include isoflavones, phenolics, terpenes, protease inhibitors, coumarins, and furanocoumarins. Using plant cell cultures it could be shown that a similar process can be observed with some alkaloidal plants, which start to produce alkaloids with antimicrobial properties (e.g., sanguinarine, canthin-6-one, rutacridone alkaloids) when challenged with elicitors from bacterial or fungal cell walls (Table XI). But what is the situation after herbivory? When plants are eaten by large herbivores, a *de novo* synthesis would be almost useless for a plant (except maybe trees), since this would not be quick enough. The situation is different, however for small herbivores such as insects or worms, which may feed on a particular plant for days or weeks. Here the *de novo* production of an allelochemical would be worthwhile. There are indeed some preliminary experimental data that support this view.

In *Liriodendron tulipifera* several aporphine alkaloids accumulate after wounding, which are otherwise not present (*506*). In tobacco the produc-

TABLE XI
INDUCTION OF ALKALOID BIOSYNTHESIS AFTER WOUNDING OR ELICITATION

Alkaloid	Plant species	Stimulus	System[a]	Ref.
Alkaloids derived from tryptophan				
Ajmalicine/ catharanthine	*Catharanthus*	Fungal elicitor	CC	*473*
Canthin-6-one	*Ailanthus*	Yeast/fungal elicitor	CC	*477*
1-Methoxycanthin-6-one	*Ailanthus*	Yeast/fungal elicitor	CC	*477*
Indole alkaloids	*Catharanthus roseus*	Fungal elicitor	CC	*472*
Alkaloids derived from phenylalanine				
Sanguinarine	*Papaver bracteatum*	Fungal elicitor	CC	*466,467*
	Papaver somniferum	Fungal elicitor	CC	*468,469*
	Eschscholtzia	Fungal elicitor	CC	*470,471*
Other types				
Atropine	*Atropa*	Wounding, herbivory	PL	*481*
Harringtonia alkaloids	*Cephalotaxus harringtonia*	Fungal elicitor	CC	*476*
Lupanine and other quinolizidine alkaloids	*Lupinus*	Wounding	PL	*482,493*
		Chemical elicitors	CC	*483,485*
Methylxanthines	*Coffea*	NaCl	CC	*478*
Nicotine	*Nicotiana*	Wounding, herbivory	PL	*479,480*
Rutacridone alkaloids	*Ruta graveolens*	Fungal elicitors	CC	*474,475*

[a] CC, Cell culture; PL, plant.

tion of nicotine, in lupines that of QAs, and in *Atropa belladonna* that of hyoscyamine are induced by wounding, thus increasing the already high levels of alkaloids by up to a factor of 5. Whereas the response was seen after 2–4 hr in lupines, it took days in *Nicotiana* and in *Atropa* (Table XI). We suggest that the wound-induced stimulation of alkaloid formation is not an isolated phenomenon, but rather an integral part of the chemical defense system.

The induced antimicrobial and antiherbivoral responses show that plants can detect environmental stress and that secondary metabolism is flexible and incorporated in the overall defense reactions. Many details on how a plant perceives and transmits information remain to be disclosed, but this will surely be a stimulating area of research in the future.

Although the physiology and metabolism of most alkaloids are extremely intricate (*38,39*) and often not known, the available data suggest that they are organized and regulated in such a way that alkaloids can fulfill their ecological defense function. In other words, the alkaloids are present at the right time, the right place, and the right concentration.

C. Importance of Alkaloids for Fitness of Plants

The aforementioned arguments strongly support the hypothesis that alkaloids serve as defense compounds for plants. Besides circumstantial evidence, we would welcome critical experiments which clearly prove that alkaloids are indeed important for the fitness and survival of the plants producing them. We suggest that if a plant species which normally produces alkaloids is rendered alkaloid-free, it should have a reduced fitness because it is much more molested by microorganims and herbivores than its alkaloid-producing counterpart.

For one group of alkaloids, the quinolizidine alkaloids, these experiments have already been performed (*2,184,484,503,527*). As mentioned before, QAs constitute the main secondary products of many members of the Leguminosae, especially in the genera *Lupinus, Genista, Cytisus, Baptisia, Thermopsis, Sophora, Ormosia,* and others (*503*).

Lupines have relatively large seeds which contain up to 40–50% protein, up to 20% lipids, and 2–8% alkaloids. To use lupine seed for animal or human nutrition, *Homo sapiens,* for several thousand years, used to cook the seeds and leach out the alkaloids in running water. This habit has been reported for the Egyptians and Greeks in the Old World, and for the Indians and Incas of the New World. The resulting seeds taste sweet, in contrast to the alkaloid-rich ones which are very bitter. In Mediterranean countries people still process lupines in the old way, and sometimes the

seeds are salted afterward and served as an appetizer, comparable to peanuts.

At the turn of the twentieth century, German plant breeders set out to grow alkaloid-free lupines, the so-called sweet lupines. Although sweet lupines are extremely rare in Nature (1 in >100,000), the efforts were largely successful, and at present, sweet varieties with an alkaloid content lower than 0.01% exist for *Lupinus albus*, *L. mutabilis*, *L. luteus*, *L. angustifolius*, and *L. polyphyllus*. As far as we know, the sweet varieties differ from the original bitter wild forms only in the degree of alkaloid accumulation. This offers the chance to test experimentally whether bitter lupines have a higher fitness than sweet ones with regard to microorganisms and herbivores.

The results of these experiments were clearcut (*2,184,503,506,527*) (Table XII). In the greenhouse, where plants are protected from herbivores or pathogens, no clear advantage was seen. When lupines were planted in the field, without being fenced in and without man-made chemical protection, however, a dramatic effect was regularly encountered, especially with regard to herbivores (*2,184,503,527*). Rabbits (*Cuniculus europaeus*) and hares (*Lepus europaeus*) clearly prefer the sweet plants and leave the bitter plants almost untouched, at least as long as there was an alternative food source. Before dying rabbits will certainly try to eat bitter lupines.

A similar picture was seen for a number of insect species, such as aphids, beetles, thrips, and leaf-mining flies (Table XII), namely, the sweet forms were attacked, whereas the alkaloid-rich ones were largely protected. The alkaloid-poor variety of *L. luteus* also became a host of *Acyrthosiphon pisii* (*506*). In Poland, where the sweet yellow lupine is one of the more important fodder plants, the invasion of the aphids became a serious problem not only because the aphid enfeebles the plants by sucking its phloem sap, but also because it transfers a viral disease. The disease, known as lupine narrow leafness, decreases seed production in infected plants, and the infection takes place early, that is, prior to the plants' blossoming. Thus, a mixed population of sweet and bitter lupines can, after a few generations, lose all sweet forms. Infestation by the aphid and the following viral infection accelerate the elimination of alkaloid-poor plants, which, even without infection, are already inferior in seed production (*506*). This observation again stresses the importance of alkaloids for the fitness of lupines.

Plant breeders have also observed that bacterial, fungal, and viral diseases are more abundant in the sweet forms, but this effect has not been documented in necessary detail.

TABLE XII
BITTER (ALKALOID-RICH) VERSUS SWEET (LOW-ALKALOID) LUPINES

Species	Lupine species	Alkaloid content	Effect	Ref.
Nonadapted herbivores				
Vertebrates				
Sheep	n.i.[a]	n.i.	Sweet lupines are preferred, bitter discriminated	*458*
Lepus europaeus	n.i.	n.i.	Sweet lupines are preferred, bitter discriminated	*459,460*
Orytolagus europaeus	*L. albus*	0.01 mg/g	Herbivory almost 100%	*2,184,527*
		2.0 mg/g	Herbivory <10%	
Insects				
Agromyzidae	*L. albus*	0.01 mg/g	Heavy infestation, 100% incidence	*2,527*
		2.0 mg/g	Infestation <1%	
		2.2 mg/g	Infestation <1%	
Sitona lineatus	*L. albus*	<0.02 mg/g	100% herbivory	*460*
		1500 mg/g	Low or no herbivory	
	L. mutabilis	2500 mg/g	Low or no herbivory	*460*
Myzus sps.	*L. luteus*	0.01 mg/g	Infestation 100%	*461*
		>0.7 mg/g	Infestation 11%	
Acyrthosiphon pisum	*Lupinus*	Sweet	High infestation	*460,462*
		Bitter	No infestation	
Aphis fabae	*L. polyphyllus*	Sweet	Infestation	*463*
		Bitter	No infestation	
Frankliniella trictici	*Lupinus*	Sweet	Heavy infestation	*464*
		Bitter	No infestation	
F. bispinosa	*Lupinus*	Sweet	Heavy infestation	*464*
		Bitter	No infestation	
Adapted herbivores				
Macrosiphum albifrons	*L. albus*	0.01 mg/g	Infestation <10%	*465*
		2.0 mg/g	Infestation 100%	
		2.2 mg/g	Infestation 100%	
	L. polyphyllus	>1 mg/g	Infestation 80%	*465*
	L. angustifolius	1.5 mg/g	Infestation 100%	*465*
	L. mutabilis	2.5 mg/g	Infestation 30%	*465*

[a] n.i., No information.

These experiments and observations clearly prove the importance of QAs for lupines, but it should not be forgotten that other secondary metabolites, such as phenolics, isoflavones, terpenes, saponins, stachyose, erucic acid, and phytic acid, are also present in lupines and may exert additional or even synergistic effects.

The lupine example also tells us about the standard philosophy and problems of plant breeding. With our present knowledge on the ecological importance of QAs for the fitness of lupines, it seems doubtful whether the selection of sweet lupines was a wise decision. In order to grow them

we have had to build fences and, worse, to employ man-made chemical pesticides, which have a number of well-documented disadvantages. It can be assumed that similar strategies, namely, breeding away unwanted chemical traits, have been followed with our other agricultural crops, with the consequence that the overall fitness was much reduced (*2*). We can easily observe the reduced fitness by trying to leave crop species to themselves in the wild: they will quickly disappear and not colonize new habitats.

There are, however, alternatives. Taking lupines as an example, we could devise large-scale technological procedures to remove alkaloids from the seeds after harvest (similar to sugar raffination from sugar beets). At present a few companies are actively exploring these possibilities. One idea is to produce pure protein, lipids, dietary fibers from bitter seeds. A spin-off product would be alkaloids, which could be used either in medicine (sparteine is exploited as a drug to treat heart arrhythmia) or in agriculture as a natural plant protective, that is, as an insecticide (*185,503*).

It is evident, however, that each plant has developed its own strategy for survival. If all plants would follow the same strategy, it would be an easy life for herbivores and pathogens, since being adapted to one species would mean adapted to all species. This specialization becomes evident if we analyze the qualitative patterns of secondary metabolite profiles present in the plant. We regularly see one to five main alkaloids in a plant, but also several (up to 80) minor alkaloids. This qualitative pattern is not constant, but differs among organs, developmental stages, individuals, populations, and species. Normally, we classify the compounds as belonging to one or two chemical groups. This does not mean, however, that their biological activities are identical. On the contrary, the addition of a lipophilic side chain to a molecule seems to be a small and insignificant variation from the chemical point of view, but this may render the compound more lipophilic, and thus more resorbable. In consequence, its toxicity may be higher (see QAs in Table I). Thus, a herbivore or pathogen has to adapt not only to one group of chemicals but to the individual compounds present. As the composition of these chemicals changes, it is even more difficult for them to cope. Therefore, we suggest that structural diversity and continuous variation are means by which Nature counteracts the adaptation of specialists.

In medicine, we do a similar thing if we want to control microbial diseases. To overcome or to prevent resistance of bacteria toward a particular antibiotic, very often mixtures of structurally different antibiotics are applied, whose molecular targets often differ. If only one antibiotic were given to all patients, the development of resistance would be much favored.

It has been argued that alkaloids cannot have a significant role in plants because not all plant species produce alkaloids (only 30% of all plants do). These authors, such as Robinson (*505*), have overlooked the fact that if all plants would produce one single alkaloid, even a very toxic alkaloid such as colchicine, it could be certain that nearly all herbivores would have developed a resistance toward this alkaloid. Only the variation of secondary metabolites, and thus of the targets which they affect, provides a means to develop efficient defense compounds. The arguments of Robinson would be correct if there were higher plants without any secondary metabolites, which, nevertheless, would thrive in Nature; however, these plants are not known. From an evolutionary perspective it is not important whether the defense chemical is an alkaloid or a terpene; it is only essential that it affect certain and important targets in herbivores or pathogens.

Although the biological activities of many alkaloids have not yet been studied and their ecological functions remain to be elucidated or proved, we can nevertheless safely say that alkaloids are neither waste nor functionless molecules, but rather they are important fitness factors, probably mostly antiherbivore compounds. Since Nature obviously favored multitasking, additional activities, such as allelopathic or antimicrobial activities, are plausible. For quinolizidine and pyrrolizidine alkaloids, these multiple functions are already well documented (Tables I–X).

D. Exceptions to the Rule: Role of Adapted Specialists

1. Microorganisms

Plants that defend themselves effectively constitute an ecological niche almost devoid of herbivores and pathogens. It is not surprising that during evolution a number of organisms evolved which have specialized on a particular host plant species and found ways to tolerate, or even to exploit, the defense chemistry of their hosts (*4,10–22*). As compared to the huge number of potential enemies, the number of adapted specialists is usually small, and in general a "status quo" or equilibrium can be observed between the specialists (or parasites) and their hosts. A specialist is not well advised to kill its host, since this would destroy its own resources; a mutualism is more productive for survival.

Host plant-specific specialists occur within bacteria, fungi, and herbivores. The interaction of the former two groups is a central topic for plant pathologists. They often find that susceptible and nonsusceptible microbe strains exist. In most cases, it is not known how these microbial specialists achieved a relationship with the host plant chemistry, for example, whether they degrade secondary metabolites or whether they simply toler-

ate them. Many phytopathogenic bacteria and fungi produce their own secondary metabolites, which are often toxic to plants. It is assumed that these phytotoxins serve to weaken the host plants' defense, but may be this is not the whole story.

Many grasses are infected with fungi that produce ergot alkaloids. It has been assumed that these fungi (e.g., *Claviceps*) are proper parasites. In recent years, however, experimental evidence suggests that the relationship between grasses and ergot may be of a symbiotic nature (*513*). Ergot alkaloids are strong vertebrate toxins (Tables I–IV); they mimic the activity of several neurotransmitters, such as dopamine, serotonin, and noradrenaline (Table IV). In fact, the impact of herbivores on populations which were highly infected by fungi was more reduced than those without. This means that the fungi exploit the nutrients of their host plants and supply them with strong poisons, which are not produced by the plants themselves. Since the fungi do not kill their hosts, this close interrelationship seems to be of mutual interest. We expect that similar relationships are likely to be detected in the future.

2. *Insect Herbivores*

As mentioned earlier, a large number of mono- and oligophagous insects exist which have adapted to their host plants and the respective defense chemistry in complex fashions. In general, we can see the following main schemes (*4,15,17,32,507,508*). In Type 1 adaptations, a species "learns" (or, as we should say, during evolution variants have been selected by natural selection which can tolerate a noxious defense compound) (a) by finding a way to avoid its resorption in the gut; (b) if resorption cannot prevented, by eliminating the toxin quickly via the Malpighian tubules or degrading it by detoxifying microsomal and other enzymes; and (c) by developing a target site that is resistant to the toxin, such as a receptor which no longer bind the exogenous ligand. Alternatively, in Type 2 strategies a species not only tolerates a plants' defense compound, but exploits it for its own defense or for other purposes, such as pheromones (*4,17,494–496,506*).

Examples of Type 1 include *Manduca sexta*, whose larvae live on *Nicotiana* and other solanaceous plants. The alkaloids present in these plants, such as nicotine or hyoscyamine, are not stored but are degraded or directly eliminated with the feces (*182*). In addition, it has been postulated that nicotine may either not diffuse into nerve cells or that the acetylcholine recpetor no longer binds nicotine as in "normal" animals (*17*). The potato beetle (*Leptinotarsa decemlineata*) lives on *Solanum* species containing steroid alkaloids, which are tolerated, but not stored, by this species. The bruchid beetle *Callosobruchus fasciatus* predates

seeds of QA-rich plants, such as *Laburnum anagyroides;* this beetle eliminates most of the dietary cytisine with the feces (*492*).

Examples of Type 2 are to some degree more interesting. In a number of plants alkaloids are translocated via the phloem (*511*). When aphids live on these plants they are in direct contact with the alkaloids present. A number of examples are known at present which show that adapted aphids can store the dietary alkaloids. Examples are the quinolizidines in *Aphis cytisorum, A. genistae,* and *Macrosiphum albifrons,* the pyrrolizidines in *Aphis jacobaea, A. cacaliaster,* and aconitine in *Aphis aconiti* (*185,511*). For alkaloid-storing *M. albifrons* it was shown experimentally that the QAs stored provide protection against carnivorous beetles, such as *Carabus problematicus* or *Coccinella septempunctata* (*465,503*). *Acyrthosiphon spartii* prefers sparteine-rich *Cytisus scoparius* plants (*506*); although it is likely that this species also stores QAs, it has not been demonstrated to do so.

Larvae of the pyralid moth *Uresiphita reversalis* live on QA-producing plants, such as *Teline monspessulana.* The larvae store some of the dietary alkaloids, especially in the integument and also the silk glands. The uptake is both specific and selective and is achieved by a carrier mechanism. Whereas alkaloids of the 10-oxosparteine type dominate in the plant, it is the more toxic cytisine that is accumulated by the larvae, with the 10-oxosparteines being eliminated with the feces (*503,514*). The larvae gain some protection from storing QAs, as was shown in experiments with predatory ants and wasps. When the larvae pupate, most of the alkaloids stored are used to impregnate the silk of the cocoon, thereby providing defense for this critical developmental stage (*503,514*). The emerging moth lives cryptically, has no aposematic coloring, and does not contain alkaloids. In contrast the alkaloid-rich larvae are aposematically colored and live openly on the plants (*503,514*).

The larvae of the blue butterfly (*Plebejus icaroides*) feed only on lupines, rich in alkaloids. As far as we know, the larvae do not sequester or store the dietary alkaloids (*506*). *Helopeltis* feeds on *Cinchona* bark, which is rich in cinchonine-like alkaloids; it stores and uses them for its own defense (*506*). Larvae of the butterflies *Pachlioptera aristolochiae, Zerynthia polyxena, Ornithoptera priamus,* and *Battus philenor* live on *Aristolochia* plants and were shown to take up and sequester aristolochic acid, a carcinogenic alkaloid discussed earlier, as an effective defense compound (*4,28,236*).

The best-studied group of acquired alkaloids are the pyrrolizidines, which are produced by plants, especially in the families Asteraceae and Boraginaceae (*502*). Some arctiid larvae of *Tyria jacobaea, Cycnia mendica, Amphicallia bellafrix, Arginia cribaria,* and *Arctia caja* were shown

to store the dietary PAs and exploit them for their own defense (*4,17,28,31,222–224,237*). In *Tyria jacobaea, Arctia caja, Diacrisia sannio, Phragmatobia fuligonosa,* and *Callimorpha dominula* PAs are taken up and stored in the integument (*523*).

Monarch butterflies (e.g., *Danaus plexipus*) combine two sets of natural compounds. Larvae feed on plants rich in cardiac glycosides and use them as chemical defense compounds. Adult butterflies visit plants with PAs, where they collect PAs that are converted to pheromones or transferred to their eggs (*4,17,31,33,361,515*). A similar PA utilization scheme was observed with larvae of the moth *Utetheisa ornatrix* (*367,516*), where the compounds were shown to be deterrent for spiders and birds (*225, 525*). The chrysomelid beetle *Oreina* feeds on PA-containing plants, such as *Adenostyles,* and stores the dietary PAs in the defense fluid (*463,524*).

In the arctiid *Creatonotos transiens* was observed an advanced exploitation of PAs (*31,33,429,517–521*). The alkaloids are phagostimulants for larvae, which are endowed with specific alkaloid receptors. Dietary pyrrolizidine *N*-oxides are resorbed by carrier-mediated transport. After resorption, free PAs are converted to the respective *N*-oxides and (7*S*)-heliotrine to (7*R*)-heliotrine. The latter form is later converted to a male pheromone, (7*R*)-hydroxydanaidal. PAs are stored in the integument, where they serve as defense compounds and are not lost during metamorphosis. In the adult moth, however, the PAs are mobilized. In the female adult, PAs are translocated into the ovary and subsequently into the eggs. In the male, PAs are necessary for the induction of abdominal scent organs and concomitantly for the biosynthesis of PA-derived pheromones, which are dissipated from these coremata. In addition, PAs are transferred into the spermatophore and thus donated to the female. A significant amount of PAs is further transferred to the eggs, which thus obtain chemical protection from the PAs previously acquired by both male and female larvae.

Marine dinoflagellates produce a number of toxins, such as saxitoxin, surugatoxin, tetrodotoxin, and gonyautoxin, that affect ion channels (Table IV). These algae are eaten by some copepods, fish, and molluscs that also store these neurotoxins (*4,17,28,29,494,495*). As a consequence, these animals have acquired chemical defense compounds, which they can use against predators.

This discussion is not meant to be complete, but should illustrate that a number of insect herbivores exploit the chemistry of their food plants. These insects are adapted and have evolved a number of molecular and biochemical traits that can be considered as prerequisites. However, many of the respective plant–insect interactions have not yet been studied, and

it is therefore likely that the acquisition of dietary defense compounds is even more widely distributed in Nature than anticipated.

3. Vertebrate Herbivores

Whereas insect herbivores are often highly host plant specific, vertebrate herbivores tend to be more of the polyphagous type, although some specialization may occur. For example, grouse (*Lagopus lagopus*) or capercaillies (*Tetrao urogallus*) prefer plants of the families of Ericaceae or Coniferae, and crossbills seeds of *Picea* and *Abies* species, which are rich in terpenes. The Australian koala is oligophagous and prefers terpene-rich species of the genus *Eucalyptus*.

For approximately 65 million years, the only true herbivorous vertebrates have been the mammals. The Mesozoic reptiles disappeared following the mesophytic flora. Birds, though a few species feed on seeds and berries, seldom eat leaves (except geese and grouse), and they frequently use insects, in addition to plant parts, as a food source (*18*).

Although a single plant can be a host for hundreds of insect larvae, hundreds of plants comprise a daily menu for a larger mammal. The strategies of the polyphagous species include the following.

1. Avoidance of plants with very toxic vertebrate poisons (these species are usually labeled toxic or poisonous by man) by olfaction or taste discrimination. Often such compounds may be described as bitter, pungent, bad smelling, or in some other way repellent.
2. Sampling of food from a wide variety of sources and thus minimizing the ingestion of high amounts of a single toxin.
3. Detoxification of dietary alleochemicals, which can be achieved by symbiotic bacteria or protozoa living in the rumen or intestines, or by liver enzymes which are specialized for the chemical modification of xenobiotics. This evolutionary trait is very helpful for *Homo sapiens*, since it endowed us with a means to cope with our man-made chemicals which pollute the environment. Carnivorous animals, such as cats, are known to be much more sensitive toward plant poisons (*505*). It was suggested that these animals, which do not face the problem of toxic food normally, are thus not adapted to the handling of allelochemicals.
4. Some animals, such as monkeys, parrots, or geese, ingest soil. For geese (*185*) it was shown that the ingested soil binds dietary allelochemicals, especially alkaloids (*185*). This procedure would reduce the allelochemical content available for resorption.
5. Animals are intelligent and can learn. The role of learning in food and toxin avoidance should not be underestimated, but it has not been studied in most species.

For most vertebrate herbivores, the ways they manage to avoid, tolerate, or detoxify their dietary allelochemicals have not been explored. Sometimes, only domesticated animals were used in experiments, but they tend to make more mistakes in food choice than the wild animals.

More evidence on this subject is available for *Homo sapiens,* who has evolved a number of "tricks," some of them obviously not anticipated by evolution. First, man tends to avoid food with bitter, pungent, or strongly scented ingredients. As a prerequisite he needs corresponding receptors in the nose or on the tongue which evolved during the long run of evolution as a means to avoid intoxication. Second, our liver still contains a set of detoxifying enzymes which can handle most xenobiotics. Furthermore, some of these enzymes, such as cytochrome *P*·450 oxidase, is inducible by dietary xenobiotics. Third, besides these biological adaptations, man has also used his brain to avoid plant allelochemicals. (a) Many fruits or vegetables are peeled. As many alkaloids and other compounds are stored in the epidermis, for example, steroid alkaloids in potato tubers or cucurbitacins in cucurbits, peeling eliminates some of these compounds from consumption. (b) Most food is boiled in water. This leads to the thermal destruction of a number of toxic allelochemicals, such as phytohaemagglutinins, protease inhibitors, and some esters and glycosides. Many water-soluble compounds are leached out into the cooking water and are discarded after cooking (e.g., lupines or potatoes). (c) South American Indians ingest clay when alkaloid-rich potato tubers are on the menu. Since clay binds steroidal alkaloids, geophagy is thus an ingenious way to detoxify potential toxins in the diet (*522*). (d) Man has modified the composition of allelochemicals in his crop plants, in that unpleasant taste components have been reduced by plant breeding. From the point of view of avoidance, this strategy is plausible, but, as was discussed earlier, it is deleterious from the point of view of chemical ecology. These plants often lose their resistance against herbivores and pathogens, which then has to be replaced by man-made pesticides.

In general, only a few plants are exploited by man as food, as compared to the 300,000 species present on our planet. This means that even *Homo sapiens* with all his ingenuity has achieved only a rather small success, indicating the importance and power of chemical plant defenses.

4. Alkaloid Production by Animals

In this context, it is worth recalling that a number of animals are able to synthesize their own defense compounds, among them several alkaloids (*4,17,28,494–496*). These animals have the common feature that they are usually slow-moving, soft-bodied organisms. Marine animals, such as mol-

luscs, sponges, zooanthids, and fishes, have been shown to contain a variety of alkaloids, such as acrylcholine, neosaxitoxin, murexin, pahutoxin, palytoxin, petrosine, and tetramine, that are toxic to other animals (*4,17,28,29,221,226,229,232,233,234,495*).

A number of nemertine worms, such as *Amphiporus* or *Nereis*, produce alkaloids such as 2,3-bipyridyl, anabaseine, nemertelline, or nereistoxin, which are toxic to predators such as crayfish (*4,17,28,230,226,*). Arthropod-made alkaloids include glomerine and homoglomerine in *Glomerus* (*215*), adaline in *Adalia* (*227*), coccinelline, euphococcinine, and derivatives in *Coccinella, Epilachna,* and other coccinellid beetles (*28,226,227,235*), and stenusine in *Stenus* (*215*), which are considered to be antipredatory compounds (*4,17,28,494–496*).

Solenopsis ants produce piperidine alkaloids which resemble the plant alkaloid coniine. These alkaloids are strong deterrents and inhibit several cellular processes, such as electron transport chains (Table IV) (*28,494*). Many insects indicate the content of toxic natural products by warning colors (aposematism) or by the production of malodorous pyrazines (*4,17,231,494*).

Not only are lower animals able to synthesize alkaloids, but also vertebrates, especially in the class Amphibia. Tree frogs of the genus *Dendrobates* accumulate steroidal alkaloids, such as batrachotoxin, pumiliotoxins A–C, gephyrotoxin, and histrionicotoxin, in their skin, which are strong neurotoxins (Table IV) (*4,17,28*). Natives have used the alkaloids as arrow poisons. Similar alkaloids (i.e., homobatrachotoxin) have recently been detected in passerine birds of the genus *Pitohui* (*528*). Salamanders, *Salamandra maculosa,* which are aposematically colored, produce the toxic salamandrine and derivatives, alkaloids of the steroidal group (*4,17,28*). Salamandrine is both an animal toxic (paralytic) and an antibiotic. Toads (Bufonidae) produce in their skin cardiac glycosides of the bufadienolide type, but also a set of alkaloids, such adrenaline, noradrenaline, adenine, bufotenine, or bufotoxin (*4,17,28*). Except for bufotoxin, the other chemicals are, or mimic, neurotransmitters.

These examples show that alkaloids found in animals can either be derived from dietary sources (see Section III,D,2) or be made endogenously. Common to both origins is their use as chemical defense compounds, analogous to the situation found in plants. In animals we can observe the trend that sessile species, such as sponges and bryozoans, or slow-moving species without armor, such as worms, nudibranchs, frogs, toads, and salamanders, produce active allelochemicals (*28,29,494,495*), but not so those with weapons, armor, or the possibility for an immediate flight. Plants merely developed a similar strategy as these "unprotected"

animal species. In this context it seems amazing that hardly anybody has doubted the defensive role of alkaloids in animals, whereas people did, and still do, where alkaloids in plants are concerned.

IV. Conclusions

Evidence is presented in this overview that alkaloids are not waste products or functionless molecules as formerly assumed (*34,35*), but rather defense compounds employed by plants for survival against herbivores and against microorganisms and competing plants. These molecules were obviously developed during evolution through natural selection in that they fit many important molecular targets, often receptors, of cells (i.e. they are specific inhibitors or modulators), which can clearly be seen in molecules that mimic endogenous neurotransmitters (Table IV; Section II,A,3,a).

On the other hand, microorganisms and herbivores rely on plants as a food source. Since both have survived, there must be mechanisms of adaptations toward the defensive chemistry of plants. Many herbivores have evolved strategies to avoid the extremely toxic plants and prefer the less toxic ones. In addition, many herbivores have potent mechanisms to detoxify xenobiotics, which allows the exploitation of at least the less toxic plants. In insects, many specialists evolved that are adapted to the defense chemicals of their host plant, in that they accumulate these compounds and exploit them for their own defense. Alkaloids obviously function as defense molecules against insect predators in the examples studied, and this is further support for the hypothesis that the same compound also serves for chemical defense in the host plant.

The overall picture of alkaloids and their function in plants and animals seems to be clear, but we need substantially more experimental data to understand fully the intricate interconnections between plants, their alkaloids, and herbivores, microorganisms, and other plants.

Acknowledgments

The work of the author was supported by the Deutsche Forschungsgemeinschaft. I thank Dr. Th. Twardowski for reading an earlier draft of the manuscript.

REFERENCES

1. M. Edmunds, "Defense in Animals," Longmans, Harlow, New York, 1974.
2. M. Wink, *Theor. Appl. Genet.* **75,** 225 (1988).
3. D. A. Levin, *Annu. Rev. Ecol. Syst.* **7,** 121 (1976).
4. J. B. Harborne, "Introduction to Ecological Biochemistry," 3rd Ed. Academic Press, London, New York, 1988.
5. E. Wollenweber, *Naturwissenschaften* **76,** 458 (1989).
6. H. Kauss, *J. Cell Sci* **2** (Suppl.), 89 (1985).
7. B. J. Deverall, "Defense Mechanisms in Plants," Cambridge Univ. Press, Cambridge, London, 1977.
8. T. Boller and A. Wiemken, *Annu. Rev. Plant Physiol.* **37,** 137 (1986).
9. M. Wink, *Naturwissenschaften* **71,** 635 (1984).
10. G. Fraenkel, *Science* **129,** 1466 (1959).
11. J. B. Harborne, *Nat. Prod. Rep.* **3,** 323 (1986).
12. H. Z. Levinson, *Experientia* **32,** 408 (1976).
13. A. Nahrstedt, *Plant Syst. Evol.* **150,** 35 (1985).
14. G. A. Rosenthal, "Plant Nonprotein Amino Acids and Imino Acids," Academic Press, London, New York, 1982.
15. G. A. Rosenthal and D.H. Janzen, "Herbivores: Their Interaction with Secondary Plant Metabolites," Academic Press, London, New York, 1979.
16. H. Schildknecht, *Comment.-Pontif. Acad. Sci.* **3,** 59 (1977).
17. D. Schlee, "Ökologische Biochemie," Springer-Verlag, Berlin, Heidelberg, New York, 1986.
18. T. Swain, *Annu. Rev. Plant Physiol.* **28,** 479 (1977).
19. G. R. Waller, "Allelochemicals: Role in Agriculture and Forestry," American Chemical Society, Symp. Ser., Vol. 330, Washington, D.C., 1987.
20. R. H. Whittaker and R. P. Feeney, *Science* **171,** 757 (1971).
21. T. Hartmann, *Plant Syst. Evol.* **150,** 15 (1985).
22. H. Grisebach and J. Ebel, *Angew. Chem.* **90,** 668 (1978).
23. C. J. W. Brooks, and D. G. Watson, *Nat. Prod. Rep.* **2,** 427 (1985).
24. U. Eilert, *in* "Cell Culture and Somatic Cell Genetics of Plants" (F. Constabel and I. K. Vasil, eds.), Vol. 4, p. 153. Academic Press, London, New York, 1987.
25. M. Wink, *in* "Cell Culture and Somatic Cell Genetics of Plants" (F. Constabel and I. K. Vasil, eds.), Vol. 4, p. 17. Academic Press, London, New York, 1987.
26. R. A. Dixon, and C. L. Lamb, *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **41,** 339 (1990).
27. P. R. Ehrlich and P. H. Raven, *Evolution* **18,** 586 (1964).
28. G. Habermehl, "Gifttiere und ihre Waffen," Springer-Verlag, Berlin, Heidelberg, 1983.
29. D. Mebs, "Gifte im Riff" Wiss. Verlagsgesellschaft, Stuttgart, 1989.
30. A. Nahrstedt, *Planta Med.* **55,** 333 (1989).
31. D. Schneider, *in* "Perspectives in Chemoreception Behavior," (R. F. Chapman and E. A. Bernays, eds.), p. 123. Springer-Verlag, Berlin, New York.
32. M. Wink and D. Schneider, *J. Comp. Physiol. B* **160,** 389 (1990).
33. M. Boppé, *Naturwissenschaften* **73,** 17 (1986).
34. K. Paech, "Biochemie und Physiologie der sekundären Pflanzenstoffe." Springer-Verlag, Berlin, Heidelberg, 1950.
35. K. Mothes, *Rec. Adv. Phytochem.* **10,** 385 (1976).

36. M. Wink and L. Witte, *Planta* **161,** 519 (1984).
37. M. Wink and L. Witte, *Z. Naturforsch.* **40C,** 767 (1985).
38. K. Mothes and H. R. Schütte, "Biosynthese der Alkaloide." VEB Deutsch. Verlag Wiss., Berlin, 1969.
39. K. Mothes, H. R. Schütte, and M. Luckner, "Biochemistry of Alkaloids." Verlag Chemie, Weinheim, Germany, 1985.
40. D. R. Dalton, "The Alkaloids: The Fundamental Chemistry." Dekker, New York, 1979.
41. J. S. Yang, S. R. Luo, X. L. Chen, and Y. X. Li, *Yaoxue Xuebao* (*Acta Pharmacol. Sin.*) **14,** 167 (1979).
42. R. Verpoorte, *In* "Antiseptika" (A. Kramer, W. Weuffen, A. P. Krasilmikov, D. Groeschel, E. Bulka, and D. Rehn, eds.), Vol. 2, p. 385. VEB Verlag Volk und Gesundheit, Berlin, 1987.
43. R. Verpoorte, T. A. van Beek, P. Thomassen, J. Aandewiel, and A. Baerheim Svendsen, *J. Ethnopharmacol.* **8,** 287 (1983).
44. P. Perera, F. Sandberg, T. A. van Beek, and R. Verpoorte, *Phytochemistry* **24,** 2097 (1985).
45. T. A. van Beek, C. de Smidt, and R. Verpoorte, *J. Ethnopharmacol.* **14,** 315 (1985).
46. T. A. van Beek, R. Verpoorte, A. Baerheim-Svendsen, and R. Fokkens, *J. Nat. Prod.* **18,** 400 (1985).
47. T. A. van Beek, F. L. C. Kuijlaars, P. H. Thomassen, R. Verpoorte, and A. Baerheim Svendsen, *Phytochemistry* **23,** 1771 (1984).
48. M. Michel, A. Lemoine, N. Dat-Xuong, and J. Olle, *C. R. Acad. Sci. Paris, Ser. D* **280,** 1493 (1975).
49. M. Michel, A. Lemoine, N. Dat-Xuong, and J. Olle, *Rev. Línst. Pasteur Lyon* **8,** 53 (1975).
50. L. A. Mitscher, R. P. Leu, M. S. Bathala, W. N. Wu, J. L. Beal, and R. White, *Lloydia* **35,** 157 (1972).
51. N. M. Rojas Hernandez, *Rev. Cubana. Med. Trop.* **31,** 199 (1979).
52. N. M. Rojas Hernandez, C. Diaz Perez, and O. Coto Perez, *Rev. Cubana Farm.* **11,** 249 (1977).
53. R. Verpoorte, E. W. Kodde, H. van Doorne, and A. Baerheim-Svendsen, *Planta Med.* **33,** 237 (1978).
54. R. H. Whitacker and R. P. Feeney, *Science* **171,** 757 (1971).
55. G. Maynart, J. L. Pousset, S. Mboup, and F. Denis, *C. R. Soc. Biol.* (*Paris*) **174,** 925 (1980).
56. M. Wink and T. Twardowski, *in* "Allelopathy: Basic and Applied Aspects" (S. J. H. Rizvi and V. Rizvi, eds.), p. 129. Chapman & Hall, London, 1992.
57. G. H. N. Towers, *J. Chem. Ecol.* **12,** 813 (1986).
58. O. O. Odebiyi and E. A. Sofowora, *Planta Med.* **36,** 204 (1979).
59. T. A. van Beek, F. L. C. Kuijlaars, P. H. A. Thomassen, R. Verpoorte, and A. Baerheim Svendsen, *Phytochemistry* **23,** 1771 (1984).
60. T. A. van Beek, R. Verpoorte, A. Baerheim-Svendsen, A. J. M. Leeuwenberg, and N. G. Bisset, *J. Ethnopharmacol.* **10,** 1 (1984).
61. K. Boakye-Viadom and S. M. Heman-Ackah, *J. Pharm. Sci.* **68,** 1510 (1979).
62. R. Verpoorte, E. Kos-Kuijck, A. Tsin A Tsoi, C. L. M. Ruigrok, G. de Jong, and A. Baerheim-Svendsen, *Planta Med.* **46,** 149 (1982).
63. R. Verpoorte, A. Tsin A Tsoi, H. van Doorne, A. Baerheim-Svendsen, *J. Ethnopharmacol.* **5,** 221 (1982).
64. C. Coune, Ph.D. Thesis University of Liege, Belgium, 1980.

65. P. Bhattacharyya, P. K. Chakrabartty, and B. K. Chowdhury, *Phytochemistry* **24,** 882 (1985).
66. R. A. Larson, K. A. Marley, R. W. Tuveson, and M. R. Berenbaum, *Photochem. Photobiol.* **48,** 665 (1988).
67. S. Ross, S. E. Megalla, D. W. Bishay, and A. H. Awad, *Fitoterapia* **6,** 309 (1980).
68. A. Al-Shamma, S. Drake, D. L. Flynn, L. A. Mitscher, Y. H. Park, G. S. Rao, A. Simpson, J. K. Swayze, T. Veysoglu, and S. T. S. Wu, *J. Nat. Prod.* **44,** 745 (1981).
69. C. Caron, M. J. Hoizey, L. Le Men-Olivier, G. Massiot, M. Zeches, C. Choisy, E. Le Magrex, and R. Verpoorte, *Planta Med.*, 409 (1988).
70. N. K. Mariee, A. A. Khalil, and A. A. Nasser, *J. Nat. Prod.* **51,** 186 (1988).
71. P. G. Waterman, *J. Nat. Prod.* **53,** 13 (1990).
72. C. Debitus and D. Laurent, *J. Nat. Prod.* **51,** 799 (1988).
73. H. Kuroda, S. Nakazawa, K. Katagiri, O. Shiratori, M. Kozuka, F. Fujitani, and M. Tomita, *Chem. Pharm. Bull.* **24,** 2413 (1976).
74. I.-L. Tsai, Y.-F. Liou, and S.-T. Lu, *Kao-hsiung I Hsueh K'o Hsueh Tsa Chih* (*Kaohsiung J. Med. Sci.*) **5,** 132 (1989).
75. W. N. Wu, J. L. Beal, G. W. Clark, L. A. Mitscher, R. P. Leu, and R. W. Doskotch, *Lloydia* **40,** 384 (1977).
76. L. A. Mitscher, W.-N. Wu, R. W. Doskotch, and J. L. Beal, *Lloydia* **35,** 167 (1972).
77. W.-N. Wu, W.-T. Liao, Z. F. Mahmoud, J. L. Beal, and R. W. Doskotch, *J. Nat. Prod.* **43,** 472 (1980).
78. W. N. Wu, J. L. Beal, G. W. Clark, L. A. Mitscher, and R. W. Doskotch, *Lloydia* **39,** 508 (1976).
79. W. N. Wu, J. L. Beal, G. W. Clark, and L. A. Mitscher, *Lloydia* **39,** 65 (1976).
80. A. Villar, J. L. Rios, and M. Mares, *Farm. Tijdschr. Belg.* **61,** 299 (1984).
81. A. Villar, M. Mares, J. L. Rios, and M. Gobernado, *Farm. Tijdschr. Belg.* **61,** 300 (1984).
82. C. D. Hufford, A. S. Sharma, and B. O. Oguntimein, *J. Pharm. Sci.* **69,** 1180 (1980).
83. C. D. Hufford, M. J. Funderburk, J. M. Morgan, and L. W. Robertson, *J. Pharm. Sci.* **64,** 789 (1975).
84. L. A. Mitscher, Y. H. Park, C. D. Clark, G. W. Clark, P. D. Hammesfahr, W. N. Wu, and J. L. Beal, *Lloydia* **41,** 145 (1978).
85. J. Lenfeld, M. Kroutil, E. Marsalek, J. Slavik, V. Preinger, and V. Simanek, *Planta Med.* **43,** 161 (1981).
86. J. Zbierska and Z. Kowalewski, *Herba Pol.* **25,** 209 (1979).
87. H. Bersch and W. Döpp, *Arzneim.-Forsch.* **5,** 77 (1955).
88. J. M. Pezzuto, S. K. Antosiak, W. M. Messmer, M. B. Slaytor, and G. R. Honig, *Chem.-Biol. Interact.* **43,** 323 (1983).
89. A. H. Amin, T. V. Subbaiah, and A. M. Abbasi, *Can. J. Microbiol.* **15,** 1067 (1969).
90. S. A. Gharbo, J. L. Beal, R. W. Doskotch, and L. A. Mitscher, *Lloydia* **36,** 349 (1973).
91. P. M. Boll, H. A. Lillevik, R. Y. Gottshall, and E. H. Lucas, *Antibiot. Ann.*, 255 (1955).
92. L. Errera, *Brussels Ac. Bull.* **13,** 272 (1887).
93. T. C. McKee and C. M. Ireland, *J. Nat. Prod.* **50,** 754 (1988).
94. L. A. Mitscher, M. S. Bathala, W. Clark, and J. L. Beal, *Lloydia* **38,** 109 (1975).
95. B. Wolters and U. Eilert, *Planta Med.* **43,** 166 (1981).
96. L. A. Mitscher, M. S. Bathala, and J. L. Beal, *Chem. Commun.* **17,** 1040 (1971).
97. W. Lwande, T. Gebreyesus, A. Chapya, C. Macfoy, A. Hassanali, and M. Okech, *Curr. Sci. Appl.* **4,** 393 (1983).
98. M. Wink, *Z. Naturforsch.* **39c,** 548 (1984).
99. S. Tyski, M. Markiewicz, K. Gulewicz, and T. J. Twardowski, *Plant Physiol.* **133,** 240 (1988).

100. G. Marquina, A. Laguna, P. Franco, L. Fernandez, R. Perrez, and O. Valiente, *Pharmazie* **44,** 870 (1989).
101. K. C. Gupta and I. C. Chopra, *Ind. J. Med. Res.* **41,** 459 (1953).
102. S. Linke, J. Kurz, and H. J. Zeiler, *Tetrahedron* **34,** 1979 (1978).
103. S. Linke, J. Kurz, and H. J. Zeiler, *Liebigs Ann. Chem.,* 1142 (1982).
104. G. Honda and M. Tabata, *Planta Med.* **36,** 85 (1979).
105. A. I. Virtanen, *Suom. Kemistil. B* **34,** 29 (1961).
106. H. M. Niemeyer, *Phytochemistry* **27,** 3349 (1988).
107. S. O. Gnan and G. M. Sherida, *J. Food Prot.* **49,** 340 (1985).
108. A. T. McPhail, D. R. McPhail, M. S. Al-Said, M. M. El-Domiaty, and F. S. El-Feraly, *Phytochemistry* **29,** 3055 (1990).
109. K. L. Rinehart, T. G. Holt, N. L. Fregeau, P. G. Keifer, G. R. Wilson, T. J. Perun, R. Sakai, A. G. Thompson, J. G. Stroh, L. S. Shield, and D. S. Seigler, *J. Nat. Prod.* **53,** 771 (1990),
110. R. Tschesche and E. Ammermann, *Chem. Ber.* **107,** 2274 (1974).
111. G. A. Charyulu, T. C. McKee, and C. M. Ireland, *Tetrahedron Lett.* **30,** 4201 (1989).
112. C. Jimenez and P. Crews, *J. Nat. Prod.* **53,** 978 (1990).
113. H. J. Preusser, G. Habermehl, M. Sablofski, and D. Schmall-Haury, *Toxicon* **13,** 285 (1975).
114. S. Ghosal, S. K. Singh, Y. Kumar, S. Unnikrsihnan, and S. Chattopadhyay, *Planta Med.,* **54,** 114 (1988).
115. B. Baumgartner, C. A. J. Erdelmeier, A. D. Wright, T. Rali, and O. Sticher, *Phytochemistry* **29,** 3327 (1990).
116. B. Wolters, *Planta Med.* **11,** 183 (1963).
117. M. S. Gil-Turnes, M. E. Hay, and W. Fennical, *Science* **246,** 116 (1989).
118. A. M. Clark, E. S. Watson, M. K. Ashfaq, and C. D. Hufford, *Pharm. Res.* **4,** 495 (1987).
119. R. H. Vallejos and O. A. Roveri, *Biochem. Pharmacol.* **21,** 3179 (1972).
120. A. Gheorghiou, E. Ionescu-Matiu, and S. Boteanu, *Comun. Bot.* **12,** 446 (1971).
121. B. Wolters, *Planta Med.* **17,** 42 (1969).
122. I. Horn and K. Steffen, *Pharm. Ztg.* **113,** 85 (1968).
123. I. Horn and K. Steffen, *Pharm. Ztg.* **113,** 945 (1968).
124. G. Kusano, A. Takahashi, K. Sugiyama, and S. Nozoe, *Chem. Pharm. Bull.* **35,** 4862 (1987).
125. B. Wolters, *Planta Med.* **19,** 189 (1970).
126. B. Wolters, *Arch. Pharm. (Weinheim, Ger.)* **297,** 748 (1964).
127. B. Wolters, *Planta Med.* **14,** 392 (1966).
128. L. A. Mitscher, H. D. H. Showalter, M. T. Shipchandler, R. P. Leu, and J. L. Beal, *Lloydia* **35,** 177 (1972).
129. Y. B. Han and W. S. Woo, *Yakhak Hoeji* **17,** 13 (1973).
130. Y. B. Han and W. S. Woo, *Yakhak Hoeji* **17,** 137 (1973).
131. L. A. Mitscher, W. N. Wu, R. W. Doskotch, and J. L. Beal, *Chem. Commun.* **11,** 589 (1971).
132. C. Wippich and M. Wink, *Experientia* **41,** 1477 (1985).
133. A. Al-Shamma, L. E. Guagliardi, L. A. Mitscher, and J. K. Swayze, *Phytochemistry* **21,** 485 (1982).
134. W. P. Cullen, R. T. LaLonde, C. J. Wang, and C. F. Wang, *J. Pharm. Sci.* **62,** 826 (1973).
135. C. D. Hufford, S. Liu, and A. M. Clark, *J. Nat. Prod.* **50,** 961 (1987).
136. B. J. Baker, P. J. Scheuer, and J. N. Shoolery, *J. Am. Chem. Soc.* **110,** 965 (1988).
137. S. W. Ayer, R. J. Anderson, C. He, and J. Clardy, *J. Org. Chem.* **49,** 3869 (1984).

138. T. Ohmoto and K. Koike, *Shoyakugaku Zasshi* **42,** 160 (1988).
139. J. B. Hudson, E. A. Graham, and G. H. N. Towers, *Photochem. Photobiol.* **43,** 21 (1986).
140. Y. Becker and U. Olshevsky, *Isr. J. Med. Sci.* **9,** 1578 (1973).
141. E. Krmpotic, N. R. Farnsworth, and W. M. Messmer, *J. Pharm. Sci.* **61,** 1508 (1972).
142. V. S. Verma and S. P. Raychaudhuri, *Acta Phytopathol. Acad. Scient. Hung.* **5,** 203 (1970).
143. M. D. Faddeeva, T. N. Belayeva, I. P. Novikov, K. G. Shalabi, and A. D. Braun, Dokl. Biochem., 250 (1980).
144. G. P. Gunawardana, S. Kohmoto, S. P. Gunasekera, O. J. McConnell, and F. E. Koehn, *J. Am. Chem. Soc.* **110,** 4858 (1988).
145. N. Yamamoto, H. Furukawa, Y. Ito, S. Yoshida, K. Maeno, and Y. Nishiyama, *Antiviral Res.* **12,** 21 (1989).
146. T. E. O'Connor, P. Schlop-Stansly, V. S. Sethi, A. Hadidi, and P. Okano, *Intervirology* **3,** 63 (1974).
147. E. Furusawa, H. Irie, D. Combs, and W. C. Wildman, *Chemotherapy* **26,** 36 (1980).
148. J. Renard-Nozaki, T. Kim, Y. Imakura, M. Kihara, and S. Kobayashi, *Res. Virol.* **140,** 115 (1989).
149. "The Merck Index," 11th Ed. Merck & Co., Rahway, New Jersey, 1989.
150. D. L. Taylor, L. E. Fellows, G. H. Farrar, R. J. Nash, D. Taylor-Robinson, M. A. Mobberley, T. A. Ryder, D. J. Jeffries, and A. S. Tyms, *Antiviral Res.* **10,** 11 (1986).
151. J. C. Cavin and E. Rodriguez, *J. Chem. Ecol.* **14,** 475 (1988).
152. A. Detzel, Diploma Thesis, University of Mainz, 1990; A. Detzel and M. Wink, *J. Chemoecology* (submitted).
153. D. H. Miles, A. M. Ly, S. A. Randle, P. A. Hedin, and M. L. Burks, *J. Agric. Food Chem.* **35,** 794 (1987).
154. V. G. Dethier and E. Bowdan, *Physiol. Entomol.* **14,** 127 (1989).
155. G. E. Zuniga and L. J. Corcuera, *Entomol. Exp. Appl.* **40,** 259 (1986).
156. G. E. Zuniga, E. M. Varanda, and L. J. Corcuera, *Entomol. Exp. Appl.* **47,** 161 (1988).
157. K. Kanehisa, H. Tsumuki, K. Kawada, and M. A. Rustamani, *Appl. Ent. Zool.* **25,** 251 (1990).
158. D. Janzen, H. Juster, and E. Bell, *Phytochemistry* **16,** 223 (1977).
159. J. S. Gill, Ph.D. Thesis, University of London (1972).
160. D. Blades and B. K. Mitchell, *Entomol. Exp. Appl.* **41,** 299 (1986).
161. L. M. Schoonhoven, *in* "Symposia of the Royal Entomological Society of London" (H. F. van Emden, ed.), Vol. 6, p. 87. Blackwell, Oxford, 1972.
162. H. Buhr, R. Toball, and K. Schreiber, *Entomol. Exp. Appl.* **1,** 209 (1958).
163. D. H. Janzen, D. G. Lynn, L. E. Fellows, and W. Hallwachs, *Phytochemistry* **21,** 1035 (1982).
164. N. B. Chatterjee and D. N. Raychaudhuri, *Zool. Pol.* **27,** 457 (1980).
165. S. R. Loomis, *Plant Physiol.* **32,** 379 (1957).
166. H. Hayashi, T. Takiuchi, S. Murao, and M. Arai, *Agric. Biol. Chem.* **53,** 461 (1989).
167. S. G. Yates, J. C. Fenster, and R. J. Bartelt, *J. Agric. Food Chem.* **37,** 354 (1989).
168. J. A. Miller and P. P. Feeney, *Ecol. Entomol.* **14,** 287 (1989).
169. A. Numata, T. Takemura, H. Ohbayashi, T. Katsuno, K. Yamamoto, K. Sato, and S. Kobayashi, *Chem. Pharm. Bull.* **31,** 2146 (1983).
170. K. Wada and K. Munakata, *J. Agric. Food Chem.* **16,** 471 (1968).
171. E. A. Bernays and R. F. Chapman, *Ecol. Entomol.* **2,** 1 (1977).
172. B. J. R. Philogene, J. T. Arnason, G. H. N. Towers, Z. Abramowski, F. Campos, D. Champagne, and D. McLachlan, *J. Chem. Ecol.* **10,** 115 (1984).

173. B. F. Devitt, B. J. R. Philogene, and C. F. Kinks, *Phytoprotection* **61,** 88 (1980).
174. W.-W. Ma, J. E. Anderson, A. T. McKenzie, S. R. Byrn, and J. L. McLaughlin, *J. Nat. Prod.* **53,** 1009 (1990).
175. E. W. Schafer, W. A. Bowles, and J. Hurlbut, *Arch. Environ. Contam. Toxicol.* **12,** 355 (1983).
176. T. Yazima and K. Munakata, *Agric. Biol. Chem.* **44,** 235 (1980).
177. B. K. Mitchell and J. F. Sutcliffe, *Physiol. Entomol.* **9,** 57 (1984).
178. K. L. S. Harley and A. J. Thorsteinson, *Can. J. Zool.* **45,** 305 (1987).
179. D. Dreyer, K. C. Jones, and R. J. Molyneux, *J. Chem. Ecol.* **11,** 1045 (1985).
180. N. D. Johnson and B. B. Bentley, *J. Chem. Ecol.* **14,** 1391 (1988).
181. M. D. Bentley, D. E. Leonard, E. K. Reynolds, S. Leach, A. B. Beck, and I. Murakoshi, *Ann. Entomol. Soc. Am.* **77,** 398 (1984).
182. M. Sauerwein, F. Sporer, P. Heidrich, and M. Wink, *J. Chem. Ecol.* (submitted).
183. M. Wink, *Proc. 3rd Int. Lupin Conf., La Rochelle, France,* 326 (1984).
184. M. Wink, *Plant Syst. Evol.* **150,** 65 (1985).
185. M. Wink, unpublished observations, 1991.
186. C. M. Adams and E. A. Bernays, *Entomol. Exp. Appl.* **23,** 101 (1978).
187. M. B. Isman and S. S. Duffey, *Entomol. Exp. Appl.* **31,** 370 (1982).
188. B. Campbell and S. S. Duffey, *J. Chem. Ecol.* **7,** 927 (1981).
189. K. Schreiber, *Entomol. Exp. Appl.* **1,** 28 (1958).
190. M. D. Bentley, D. E. Leonhard, and R. J. Bushway, *Ann. Entomol. Soc.* **77,** 401 (1984).
191. R. Kuhn and I. Low, *Angew. Chem.* **69,** 236 (1957).
192. M. Weissenberg, M. Klein, J. Meisner, and K. R. S. Ascher, *Entomol. Exp. Appl.* **42,** 213 (1986).
193. G. de Boer and F. E. Hanson, *Entomol. Exp. Appl.* **45,** 123 (1987).
194. N. Adityachaudhury, A. Bhattacharyya, A. Chowdhury, and S. Pal, *J. Sci. Ind. Res.* **44,** 85 (1985).
195. K. Richter, H. Birkenbeil, and G. Adam, *Naturwissenschaften* **76,** 333 (1989).
196. L. M. Schoonhoven and I. Derksen-Koppers, *Entomol. Exp. Appl.* **16,** 141 (1973).
197. B. C. Campbell, R. J. Molyneux, and K. C. Jones, *J. Chem. Ecol.* **13,** 1759 (1987).
198. M. D. Bentley, D. E. Leonhard, W. F. Stoddart, and L. H. Zalkow, *Ann. Entomol. Soc.* **77,** 393 (1984).
199. K. Schreiber, *Zuechter* **27,** 19 (1957).
200. K. R. Jennings, D. G. Brown, and D. P. Wright, *Experientia* **42,** 611 (1986).
201. F. El-Gayar, A. El-Shazli, S. Khafagy, and W. Watson, *Z. Angew. Entomol.* **78,** 49 (1975).
202. J. Nathanson, *Science* **226,** 184 (1984).
203. J.-K. Liu, Z.-J. Jia, D.-G. Wu, J.-Z. Wang, and Q.-G. Wang, *Phytochemistry* **29,** 2503 (1990).
204. H. C. F. Su and B. L. Sondengam, *J. Georgia Entomol. Soc.* **15,** 47 (1980).
205. M. Miyakado, I. Nakayama, H. Yoshioka, and N. Nakatani, *Agric. Biol. Chem.* **43,** 1609 (1979).
206. K. Sakata, K. Aoki, C.-F. Chang, A. Sakurai, S. Tamura, and S. Murakoshi, *Agric. Biol. Chem.* **42,** 457 (1978).
207. T. Yokata, A. Sakurai, S. Iriuchijima, and N. Takahashi, *Agric. Biol. Chem.* **45,** 53 (1981).
208. G. S. Verma, V. Ramakrishnan, N. B. Mulchandi, and M. S. Chadha, *Entomol. Exp. Appl.* **40,** 99 (1986).
209. B. P. Saxena, K. Tikku, C. K. Atal, and O. Koul, *Insect Sci. Appl.* **7,** 489 (1986).
210. P. R. Ehrlich and P. H. Raven, *Evolution* **18,** 586 (1964).

211. M. Jacobson, *Econ. Bot.* **36,** 346 (1982).
212. S. V. Evans, L. E. Fellows, T. K. M. Shing, and G. W. J. Fleet, *Phytochemistry* **24,** 1953 (1985).
213. D. Bacos, J. J. Basselier, J. P. Celerier, C. Lange, E. Marx, P. Escoubas, M. Lemaire, and J. L. Clement, *Tetrahedron Lett.* **29,** 3061 (1988).
214. B. P. Moore, W. V. Brown, and M. Rothschild, *Chemoecology* **1,** 43 (1990).
215. H. Schildknecht, *Pontif. Acad. Sci. Scr. Varia* **41,** 59 (1976).
216. K. Matsuda, M. Kimura, Komai, K., and Hamada, M., *Agric. Biol. Chem.* **53,** 2287 (1989).
217. M. Terada, M. Sano, A. Ishii, H. Kino, S. Fukushima, and T. Noro, *Nippon Yakurigaku Zasshi* (*Folia Pharmacol Jpn.*) **79,** 105 (1982).
218. M. Terada, M. Sano, A. I. Ishii, H. Kino, S. Fukushima and T. Noro, *Nippon Yakurigaku Zasshi* (*Folia Pharmacol. Jpn.*) **79,** 105 (1982).
219. M. Wink, *Z. Naturforsch.* **39C,** 553 (1984).
220. I. Kubo, T. Matsumoto, M. Kozuka, and A. Chapya, *Agric. Biol. Chem.* **48,** 2839 (1984).
221. F. Ghiretti, *Angew. Chem.* **76,** 982 (1964).
222. J. A. Edgar, P. A. Cockrum, and J. L. Frahn, *Experientia* **32,** 1535 (1976).
223. R. B. Kelley, J. N. Seiber, A. D. Jones, H. J. Segall and L. P. Brower, *Experientia* **43,** 943 (1987).
224. M. Benn, J. Degrave, C. Gnanasunderam, and R. Hutchins, *Experientia* **35,** 731 (1979).
225. T. Eisner, *in* "Insect Biology in the Future" (M. Locke, S. Smith, and T. Eisner, eds.), p. 847. Academic Press, New York, 1980.
226. T. Eisner, M. Goetz, D. Aneshansley, G. Ferstandig-Arnold, and J. Meinwald, *Experientia* **42,** 204 (1986).
227. B. Tursch, D. Daloze, M. Dupont, J. M. Pasteels, and M.-C. Tricot, *Experientia* **27,** 1380 (1971).
228. E. Y. Cheng, L. K. Cutkomp, and R. B. Koch, *Biochem. Pharmacol.* **26,** 1179 (1977).
229. J. C. Braekman, D. Daloze, P. Macedo de Abreu, C. Piccinni-Leopardi, G. Germain, and M. van Meerssche, *Tetrahedron Lett.* **23,** 4277 (1982).
230. W. R. Kem, *Am. Zool.* **25,** 99 (1985).
231. T. Guilford, C. Nicol, M. Rothschild, and B. P. Moore, *Biol. J. Linnean Soc.* **31,** 113 (1987).
232. G. H. Habermehl and H. C. Krebs, *Naturwissenschaften* **73,** 459 (1986).
233. O. R. Gottlieb, "Micromolecular Evolution, Systematics and Ecology." Springer-Verlag, Heidelberg, 1982.
234. T. Narahashi, *Physiol. Rev.* **54,** 813 (1974).
235. W. V. Brown and B. P. Moore, *Aust. J. Chem.* **35,** 1255 (1982).
236. J. von Euw, T. Reichstein, and M. Rothschild, *Isr. J. Chem.* **6,** 659 (1968).
237. R. T. Aplin, M. H. Benn, and M. Rothschild, *Nature* (*London*) **219,** 747 (1968).
238. R. D. Hagin, *J. Agric. Food Chem.* **37,** 1143 (1989).
239. D. Liu and J. V. Lovett, *Proc. Weed Seed Biol. Workshop, Organge, N. S. W.,* 116 (1987).
240. L. Overland, *Am. J. Bot.* **53,** 423 (1966).
241. M. Evenari, *Bot. Rev.* **15,** 153 (1949).
242. A. Kabarity, A. El-Bayoumi, and A. Habib, *Cytologia* **45,** 497 (1980).
243. H. Sato, Y. Kobayashi, H. Fukui, and M. Tabata, *Plant Cell Rep.* **9,** 133 (1990).
244. N. J. Walton, A. J. Parr, R. J. Robins, and M. J. C. Rhodes, *Plant Cell Rep.* **6,** 118 (1987).
245. J. V. Lovett, J. Levitt, A. M. Duffield, and N. G. Smith, *Weed Res.* **21,** 165 (1981).
246. J. V. Lovett and W. C. Potts, *Plant Soil* **98,** 137 (1987).

247. M. Wink, *Planta* **158,** 365 (1983).
248. H.-N. Chou and H.-M. Su, *in* "Phytochemical Ecology: Allelochemicals, Mycotoxins and Insect Pheromones" (C. H. Chou and G. R. Waller, eds.), p. 119. Acad. Sinica Monog. Ser., Vol. 9, (1989), Acad. Sinica, Taipei.
249. G. R. Waller, *Biol. Plant.* **31,** 418 (1989).
250. J. Friedman and G. R. Waller, *J. Chem. Ecol.* **9,** 1107 (1983).
251. M. Levi, D. Chiatante, and E. Sparvoli, *Plant Cell Rep.* **2,** 236 (1983).
252. G. R. Waller and H. Burgstrom, *Nature (London)* **222,** 576 (1969).
253. K. L. Stevens and R. J. Molyneux, *J. Chem. Ecol.* **14,** 1467 (1988).
254. D. G. Routley and J. T. Sullivan, *Agron. J.* **52,** 317 (1960).
255. F. J. Perez, *Phytochemistry* **29,** 773 (1990).
256. M. Rideau, C. Verchere, P. Hibon, J. C. Chenieux, P. Maupas, and C. Viel, *Phytochemistry* **18,** 155 (1979).
257. M. Leboeuf, A. Cavé, P. Forgacs, R. Tiberghien, J. Provost, A. Touche, and H. Jacquemin, *Plant. Med. Phytother.* **16,** 169 (1982).
258. G. Hesse, *Naturwiss. Rundsch.*, 227 (1956).
259. E. Teuscher and U. Lindequist, "Biogene Gifte." Fischer Verlag, Stuttgart, New York, 1987.
260. J. J. Kettenes-Van den Bosch, C. A. Salemink, and I. Khan, *J. Ethnopharmacol.* **3,** 21 (1981).
261. A. M. Mun, E. S. Barden, J. M. Wilson, and J. M. Hogan, *Teratology* **11,** 73 (1975).
262. C. A. Swinyard and S. Chaube, *Teratology* **8,** 349 (1973).
263. G. Habermehl, *Prog. Org. Chem.* **7,** 35 (1968).
264. D. J. O'Dowd and J. A. Edgar, *Aust. J. Ecol.* **14,** 95 (1989).
265. A. R. Mattocks, *Chem.–Biol. Interact.* **5,** 227 (1972).
266. S. Camazine, *J. Chem. Ecol.* **9,** 1473 (1983).
267. M. H. Ralphs, J. D. Olsen, J. A. Pfister, and G. D. Manners, *J. Anim. Sci.* **66,** 2334 (1988).
268. J. F. Couch, *J. Agric. Res.* **32,** 51 (1926).
269. C. F. Poe and C. C. Johnson, *Acta Pharmacol. Toxicol.* **10,** 338 (1954).
270. G. Zetler and O. Strubelt, *Arzneim.–Forsch.* **30,** 1497 (1980).
271. E. Nowacki and S. Wezyk, *Rozniki Nauk Rolnikzych* **75,** 385 (1960).
272. G. C. Lu, *Toxicol. Appl. Pharmacol.* **6,** 328 (1963).
273. W. C. Gordon and J. H. M. Henderson, *J. Agric. Sci.* **41,** 141 (1951).
274. K. Yovo, F. Huguet, J. Pothier, M. Durand, M. Breteau, and G. Narcisse, *Planta Med.*, 420 (1984).
275. D. S. Petterson, Z. C. Ellis, D. J. Harris, and Z. E. Spadek, *J. Appl. Toxicol.* **7,** 51 (1987).
276. M. Mazur, P. Polakowski, and H. Szadowska, *Acta Phys. Pol.* **17,** 299 (1966).
277. M. Mazur, P. Polakowski, and H. Szadowska, *Acta Phys. Pol.* **17,** 311 (1966).
278. O. Gessner, "Die Gift- und Arzneipflanzen in Mitteleuropa." C. Winter, Heidelberg, 1953.
279. G. A. Cordell, M. Ogura, and N. R. Farnsworth, *Lloydia* **41,** 166 (1978).
280. S. Mukhopadhyay, G. A. Handy, S. Funayama, and G. A. Cordell, *J. Nat. Prod.* **44,** 696 (1981).
281. D. G. I. Kingston, *J. Pharm. Sci.* **67,** 272 (1978).
282. R. Strauch and K. Hiller, *Pharmazie* **29,** 656 (1974).
283. S. P. Gunasekera, G. A. Cordell, and N. R. Farnsworth, *Phytochemistry* **19,** 1213 (1980).
284. A. A. Melo, C. B. Querol, A. T. Henriques, and J. A. P. Henriques, *Mutat. Res.* **171,** 17 (1986).

285. P. Rahman, I. Muhammad, C. M. Hasan, and A. Jabbar, *Bangladesh J. Bot.* **17,** 25 (1988).
286. G. A. Cordell, *Proc. Life Sci.*, 54 (1977).
287. P. Druilhe, O. Brandicourt, T. Chongsuphajaisiddhi, and J. Berthe, *Antimicrob. Agents Chemother.* **32,** 250 (1988).
288. M. Hayat, *et al.*, *Biomedicine* **21,** 101 (1974).
289. J. C. Cavin, S. M. Krassner, and E. Rodriguez, *J. Ethnopharmacol.* **19,** 89 (1987).
290. O. R. Gottlieb and W. B. Mors, *J. Agric. Food Chem.* **28,** 196 (1980).
291. M. Regina, P. Sampaio, M. M. De Oliveira, and B. Gilbert, *Cienc. Cult. (São Paulo)* **26,** 517 (1974).
292. C. W. Mosher, O. P. Crews, E. M. Acton, and L. Goodman, *J. Med. Chem.* **9,** 237 (1966).
293. G. Dreyfuss, D. P. Allais, H. Guinaudeau, and J. Bruneton, *Ann. Pharm. Fr.* **45,** 361 (1987).
294. A. Fournet, A. M. Manjon, V. Munoz, A. Angelo, J. Bruneton, R. Hocquemiller, D. Cortes, and A. Cavé, *J. Ethnopharmacol.* **24,** 337 (1988).
295. Y. Ch. Wu, Y.-F. Liou, S.-T. Lu, C.-H. Chen, J.-J. Chang, and K.-H. Lee, *Planta Med* **55,** 163 (1989).
296. J. L. Vennerstrom and D. L. Klayman, *J. Med. Chem.* **31,** 1084 (1988).
297. S. Simeon, J. L. Rios, and A. Villar, *Plant. Med. Phytother.* **23,** 202 (1989).
298. S. D. Phillips and R. N. Castle, *J. Heterocycl. Chem.* **18,** 223 (1981).
299. A. Fournet, V. Munoz, A. M. Manjon, A. Angelo, R. Hocquemiller, D. Cortes, A. Cave, and J. Bruneton, *J. Ethopharmacol.* **24,** 327 (1988).
300. V. S. Sethi, *Cancer Res.* **36,** 2390 (1976).
301. G. Dreyfuss, D. P. Allais, H. Guinaudeau, and J. Bruneton, *Ann. Pharm. Fr.* **45,** 243 (1987).
302. L. Israel, A. Depierre, and P. Chahinian, *Proc. Am. Assoc. Cancer Res.* **15,** 11 (1974).
303. A. P. Grollmann and Z. Jarkovsky, *In* "Antibiotics: Mechanism of Action of Antimicrobial and Antitumour Agents" (J. W. Corcoran, and F. E. Hahn, eds.), Vol. 3, p. 420. Springer-Verlag, Heidelberg, New York, 1975.
304. A. T. Keene, J. D. Phillipson, D. C. Warhurst, M. Koch, and E. Seguin, *Planta Med.* **53,** 201 (1987).
305. E. J. Gralla, G. L. Coleman, and A. M. Jonas, *Cancer Chemother. Rep.* **5,** 79 (1974).
306. D. K. Todorov and G. Deliconstantinos, *Experientia* **38,** 857 (1982).
307. H. Fujioka, Y. Nishiyama, H. Furukawa, and N. Kumada, *Antimicrob. Agents Chemother.* **33,** 6 (1989).
308. W. Peyer, Ph.D. Dissertation, University of Jena, Germany, 1921.
309. B. E. Cham, M. Gilliver, and L. Wilson, *Planta Med.* **53,** 34 (1987).
310. C.-N. Lin, C.-M. Lu, M.-K. Cheng, K.-H. Gan, and S.-J. Weu, *J. Nat. Prod.* **53,** 513 (1990).
311. R. Kojima, S. Fukushima, A. Ueno, and Y. Saiki, *Chem. Pharm. Bull.* **18,** 2555 (1970).
312. H. Rimpler, "Pharmazeutische Biologie II, Biogene Arzneistoffe." Thieme, Stuttgart, 1990; H. Wagner, "Pharmazeutische Biologie," 3rd Ed. Fischer, Stuttgart, 1989.
313. J. M. Cassady, W. M. Baird, and C.-J. Chang, *J. Nat. Prod.* **53,** 23 (1990).
314. R. W. Miller, R. G. Powell, and C. R. Smith, *J. Org. Chem.* **46,** 1469 (1981).
315. R. G. Powell, R. W. Miller, and C. R. Smith, *J. Chem. Soc. Chem. Commun.* 102 (1979).
316. R. G. Powell, D. Weisleder, and C. R. Smith, *J. Pharm. Sci.* **61,** 1227 (1972).
317. C. R. Smith, R. G. Powell, and K. L. Mikolajczak, *Cancer Treat Rep.* **60,** 1157 (1976).

318. Y.-H. Kuo, C.-H. Chen, L.-M. Yang Kuo, M.-L. King, T.-S. Wu, M. Haruna, and K.-H. Lee, *J. Nat. Prod.* **53,** 422 (1990).
319. S. M. Kupchan, C. W. Sigel, L. Guttman, R. J. Restivo, and R. F. Bryan, *J. Am. Chem. Soc.* **94,** 1354 (1972).
320. A. Nahrstedt, *Planta Med.* **55,** 333 (1989).
321. G. R. Pettit, V. Gaddamidi, and G. M. Craig, *J. Nat. Prod.* **47,** 1018 (1984).
322. E. Furusawa, R. H. Lockwood, S. Furusawa, M. K. M. Lum, and J. Y. B. Lee, *Chemotherapy* **25,** 308 (1979).
323. G. R. Pettit, G. M. Craig, S. B. Singh, J. A. Duke, and, D. L. Doubek, *J. Nat. Prod.* **53,** 176 (1990).
324. V. H. Ferm, *Science* **141,** 426 (1963).
325. J. Buscema, J. L. Stern, and T. R. B. Johnson, *In* "Drug Use in Pregnancy." (J. R. Niebyl, ed.), p. 89. Lea and Febiger, Philadelphia. 1987.
326. H. Paulini, R. Waibel, and O. Schimmer, *Mutat. Res.* **227,** 179 (1989).
327. M. J. Ashwood-Smith, G. H. N. Towers, Z. Abramowski, G. A. Poulton, and M. Liu, *Mutat. Res.* **102,** 401 (1982).
328. O. Schimmer and U. Leimeister, *Arch. Pharm. (Weinheim, Ger.)* **321,** 637 (1988).
329. R. F. Keeler, *J. Agric. Food Chem.* **17,** 473 (1969).
330. R. F. Keeler, S. Young, D. Brown, G. F. Stallknecht, and D. Douglas, *Teratology* **17,** 327 (1978).
331. R. F. Keeler, S. Young, and D. Brown, *Res. Commun. Chem. Pathol. Pharmacol.* **13,** 723 (1976).
332. A. M. Clark, *Mutat. Res.* **32,** 361 (1976).
333. H. Frey, personal communication, 1988.
334. R. Sivlingham and N. G. Brink, *Teratog. Carcinog. Mutagen.* **8,** 205 (1988).
335. U. Candrian, J. Luethi, U. Graf, and C. Schlatter, *Food. Chem. Toxicol.* **22,** 223 (1984).
336. M. C. Gimmler-Luz, B. Erdtmann, and R. A. Balbueno, *Mutat. Res.* **241,** 297 (1990).
337. A. L. de Paula Ramos and E. K. Marques, *Rev. Bras. Genet.* **4,** 279 (1978).
338. A. Koletsky, R. Oyasu, and J. K. Reddy, *Lab. Invest.* **38,** 352 (1978).
339. S. Avanzi, *Caryologia* **14,** 251 (1961).
340. Y. A. E. Bick and W. D. Jackson, *Aust. J. Biol. Sci.* **21,** 469 (1968).
341. R. F. Keeler, *J. Toxicol. Environ. Health* **1,** 887 (1976).
342. D. W. E. Smith, *Science* **152,** 1273 (1966).
343. M. Spatz, *Ann. N.Y. Acad. Sci.* **163,** 848 (1969).
344. G. Abel and O. Schimmer, *Hum. Genet.* **64,** 131 (1983).
345. H. Frey, F. E. Wuergler, H. Juan, C. B. Hall, and U. Graf, *Arch. Toxicol.* **56,** 158 (1985).
346. G. Robisch, O. Schimmer, and W. Goeggelmann, *Mutat. Res.* **105,** 201 (1982).
347. L. M. Hague and R. N. Jones, *Theor. Appl. Genet.* **74,** 233 (1987).
348. R. F. Keeler, *Clin. Toxicol.* **7,** 195 (1974).
349. R. F. Keeler, L. D. Balls, J. L. Shupe, and M. W. Crowe, *Cornell Vet.* **70,** 19 (1980).
350. K. E. Panter, R. F. Keeler, and W. B. Buck, *Am. J. Vet. Res.* **46,** 2064 (1985).
351. R. F. Keeler, L. D. Balls, and K. Panter, *Cornell Vet.* **71,** 47 (1981).
352. R. F. Keeler, *Clin. Toxicol.* **15,** 417 (1979).
353. D. Brusick, B. Myhr, S. Galloway, J. Rundell, D. R. Jagannath, and S. Tarka, *Mutat. Res.* **169,** 105 (1986).
354. H. W. Renner, *Experientia* **38,** 600 (1982).
355. M. Nagabhushan and S. V. Bhide, *Environ. Mutagen.* **7,** 881 (1985).
356. G. B. Panagrahi and A. R. Rao, *Cancer Lett.* **23,** 189 (1984).

357. Y. I. Sung, K. Koike, N. Tamotsu, T. Ohomoto, and U. Sankawa, *Chem. Pharm. Bull.* **32,** 1872 (1984).
358. J. Dupont, G. Dodin, and M.-A. Schwaller, *Plant Sci. Lett.* **54,** 109 (1988).
359. B. Festy, J. Poisson, and C. Paoletti, *FEBS Lett.* **17,** 321 (1971).
360. K. Gerzon and G. H. Svoboda, *in* "The Alkaloids" (A. Brossi, ed.), Vol. 21, p. 1. Academic Press, New York, 1983.
361. J. A. Edgar, M. Boppre, and D. Schneider, *Experientia* **35,** 1447, (1979).
362. R. A. Larson and K. A. Marley, *Phytochemistry* **23,** 2351 (1984).
363. T. M. Wada and C. G. Whiteley, *Biochem. Int.* **14,** 189 (1987).
364. D. R. Curtis and G. A. R. Johnston, *in* "Neuropoisons: Their Pathophysiological Activity," (L. L. Simpson and D. R. Curtis, eds.), Vol. 2, p. 207. Plenum Press, New York, London.
365. R. Wu, A. Kumar, and J. R. Warner, *Proc. Natl. Acad. Sci. U.S.A.* **68,** 3009 (1971).
366. L. Recher, H. Chan, L. Briggs, and N. Parry, *Cancer Res.* **32,** 2495 (1972).
367. J. J. C. Culvenor and J. A. Edgar, *Experientia* **28,** 627 (1972).
368. K. W. Mohn, M. J. Waring, D. Glaubiger, and C. A. Friedman, *Cancer Res.* **35,** 71 (1975).
369. M. Gosalvez, M. Blanco, J. Hunter, M. Miko, B. and Chance, *Eur. J. Cancer* **10,** 567 (1974).
370. D. C. U'Prichard, *Adv. Biochem. Psychopharmacol.* **23,** 103 (1980).
371. J. G. Cannon, *Annu. Rev. Pharmacol. Toxicol.* **23,** 103 (1983).
372. Y. Pichon, J. Schmittmayer, and W. Ulbricht, *Neurosci. Lett.* **22,** 325 (1981).
373. T. S. Papas, L. Sandhouse, M. A. Chirigos, and E. Furusawa, *Biochem. Biophys. Res. Commun.* **52,** 88 (1973).
374. C. S. Andreo, E. G. Orellano, and H. M. Niemeyer, *Z. Naturforsch.* **39c,** 746 (1984).
375. M. Canessa, E. Jaimovich, and M. de la Fuente, *J. Membr. Biol.* **13,** 263 (1973).
376. H. Zollner, "Handbook of Enzyme Inhibitions." Verlag Chemie, Weinheim, Germany, 1989.
377. R. J. Dowson, A. N. Clements, and T. E. May, *Neuropharmacology* **14,** 235 (1975).
378. G. Duportail and H. Lami, *Biochim. Biophys. Acta* **402,** 20 (1975).
379. M. Caprasse and C. Houssier, *Biochimie* **65,** 157 (1983).
380. V. K. Akimenko, A. G. Kozlovskii, A. G. Medentsev, N. P. Golovchenko, and M. U. Arinbasarov, *Biokhimiya (Moscow)* **41,** 2220 (1976).
381. D. C. Warhurst, *J. Antimicrob. Chemother.* **18B,** 51 (1986).
382. J. Walden and E.-J. Speckmann, *Neurosci. Lett.* **27,** 139 (1981).
383. B. K. Mitchell, *J. Chem. Ecol.* **13,** 2009 (1987).
384. L. Wilson, J. R. Bamburg, S. B. Mizel, L. M. Grisham, and K. M. Creswell, *Fed. Proc.* **33,** 158 (1974).
385. J. C. Lee, D. Harrison, and S. N. Timasheff, *Biophys. J.* **14,** 75a (1975).
386. L. Wilson, K. Anderson, and D. Chin, *Cold Spring Harbor Conf. Cell Proliferation* **3C,** 1051 (1976).
387. P. Warnecke and S. Seeber, *Z. Krebsforsch.* **73,** 67 (1969).
388. F. E. Samson, *Annu. Rev. Pharmacol. Toxicol.* **16,** 143 (1976).
389. C. Melchior and M. A. Collins, *Crit. Rev. Toxicol.* **9,** 313 (1982).
390. A. A. Kraevskii, *Sov. J. Bioorg. Chem. (Engl. Transl.)* **4,** 615 (1979).
391. A. Beld and E. Ariens, *Eur. J. Pharmacol.* **25,** 203 (1974).
392. T. Schewe and W. Müller, *Acta Biol. Med. Ger.* **35,** 1019 (1976).
393. N. Kakiuchi, M. Hattori, H. Ishii, and T. Namba, *Planta Med.*, 22 (1987).
394. T. Sato, Y. Kanaho, and T. Fujii, *Cell Struct. Funct.* **5,** 155 (1980).
395. M. L. Sethi, *J. Pharm. Sci.* **72,** 538 (1983).

396. E. Smekal and N. Kubova, *Stud. Biophys.* **92,** 73 (1982).
397. M. Maiti and K, Chaudhuri, *Indian J. Biochem. Biophys.* **18,** 245 (1981).
398. A. K. Krey and F. E. Hahn, *Science* **166,** 755 (1969).
399. N. Nakai, Y. Fujii, K. Kobashi, and K.Nomura, *Arch. Biochem. Biophys.* **239,** 491 (1985).
400. E. Smekal, N. Kubova, V. Kleinwächter, and M. Cushmann, *Studia Biophys.* **114,** 257 (1986).
401. M. L. Sethi, *Can. J. Pharm. Sci.* **16,** 29 (1981).
402. J. J. Neal, *Phytochemistry* **28,** 451 (1989).
403. M. L. Sethi, *J. Nat. Prod.*, **42,** 187 (1979); V. S. Sethi and M. L. Sethi, *Biochem. Biophys. Res. Commun.* **63,** 1070 (1975).
404. R. S. Gupta and L. Siminovitch, *Biochemistry* **16,** 3209 (1977).
405. R. L. Irwin and H. J. Smith, *Biochem. Pharmacol.* **3,** 147 (1960).
406. L. Triner, Y. Vulliemoz, J. Schwartz, and G. G. Nahas, *Biochem. Biophys. Res. Commun.* **40,** 64 (1970).
407. R. H. Vallejos, *Biochim. Biophys. Acta* **292,** 193 (1973).
408. R. S. Gupta, *Biochem. Pharmacol.* **30,** 3039 (1981).
409. M. Maiti, R. Nandi, and K. Chaudhuri, *FEBS Lett.* **142,** 280 (1982).
410. S. V. Evans, L. E. Fellows, and E. A. Bell, *Phytochemistry* **22,** 768 (1983).
411. R. J. Molyneux, J. N. Roitman, G. Dunnheim, T. Szumilo, and A. D. Elbein, *Arch. Biochem. Biophys.* **251,** 450 (1986).
412. P. L. Durham and J. E. Poulton, *Plant Physiol.* **90,** 48 (1990).
413. G. C. Kite, L. E. Fellows, G. W. J. Fleet, P. S. Liu, A. M. Scofield, and N. G. Smith, *Tetrahedron Lett.* **29,** 6483 (1988).
414. D. Davis, P. Schwarz, T. Hernandez, M. Mitchell, B. Warnock, and A. D. Elbein, *Plant Physiol.* **76,** 972 (1984).
415. D. Young and I. T. Oliver, *Biochemistry* **7,** 3231 (1968).
416. M. Ohta and T. Narahashi, *J. Pharmacol. Exp. Ther.* **187,** 47 (1973).
417. A. Korcz, M. Markiewicz, J. Pulikowska, and T. Twardowski, *J. Plant Physiol.* **128,** 433 (1987).
418. A. L. Kleinhaus, *J. Physiol. (London)* **299,** 309 (1980).
419. G. Paolisso, M. Nenquin, W. Schmeer, F. Mathot, H. P. Meissner, and J. C. Henquin, *Biochem. Pharmacol.* **34,** 2355 (1985).
420. M. Ishida and H. Shinozaki, *Br. J. Pharmacol.* **82,** 523 (1984).
421. T. Zwierzynski, A. Joachimak, M. Barciszewska, K. Kulinska, and J. Barciszewski, *Chem.–Biol. Interact.* **42,** 107 (1982).
422. A. Korcz, M. Markiewicz, J. Pulikowska, and T. Twardowski, *J. Plant Physiol.* **128,** 433 (1987).
423. P. J. Shubat, R. J. Bowers, and R. J. Huxtable, *J. Pharmacol. Exp. Ther.* **252,** 70 (1990).
424. M. J. Mahmoud, F. Redha, M. J. Al-Azawi, W. A. Hussein, and Y. T. Behnam, *J. Biol. Sci. Res.* **18,** 127 (1986).
425. C. C. J. Culvenor, D. T. Downing, J. A. Edgar, and M. V. Jago, *Ann. N.Y. Acad Sci.* **163,** 837 (1969).
426. A. R. Mattocks and R. Jukes, *Chem.–Biol. Interact.* **75,** 225 (1990).
427. A. K. Dwivedy, *Comp. Biochem. Physiol. C: Comp. Pharmacol. Toxicol.* **91C,** 349 (1988).
428. C. W. Myers and J. W. Daly, *Am. Mus. Novit.* **0(2692),** 1 (1980).
429. D. Schneider, M. Boppre, J. Zweig, S. B. Horsley, T. W. Bell, J. Meinwald, K. Hansen, and E. W. Diehl, *Science* **215,** 1264 (1982).
430. J. G. Roddick, A. L. Rijnenberg, and S. F. Osman, *J. Chem. Ecol.* **14,** 889 (1988).

431. J. G. Roddick, *Phytochemistry* **28,** 2631 (1989).
432. R. J. Bushway, S. A. Savage, and B. S. Ferguson, *Am. Potato J.* **64,** 409 (1987).
433. J. G. Roddick and A. L. Rijnenberg, *Physiol. Plant.* **68,** 436 (1986).
434. G. Kusano, A. Takahashi, K. Sugiyama, and S. Nozoe, *Chem. Pharm. Bull.* **35,** 4862 (1987).
435. J. A. Roddick, A. L. Rijnenberg, and M. Weissenberg, *Phytochemistry* **29,** 1513 (1990).
436. P. Berger, J. D. Elsworth, M. E. A. Reith, D. Tanen, and R. H. Roth, *Eur. J. Pharmacol.* **176,** 251 (1990).
437. D. H. Williams, M. J. Stone, P. R. Hauck, and S. K. Rahman, *J. Nat. Prod.* **52,** 1189 (1989).
438. R. B. Koch, D. Desaiah, D. Foster, and K. Ahmed, *Biochem. Pharmacol.* **26,** 983 (1977); S. Carson, S. Godwin, J. Massoulie, and G. Kato, *Nature (London)* **266,** 176 (1977).
439. Y. Monsereenusorn and T. Glinsukon, *Toxicol. Lett.* **4,** 399 (1979).
440. Y. Shimomura, T. Kawada, and M. Suzuki, *Arch. Biochem. Biophys.* **270,** 573 (1989).
441. W. D. Wilson, A. N. Gough, and J. J. Doyle, *J. Med. Chem.* **19,** 1261 (1976).
442. S. Artvinli, *Cytologia,* **52,** 189 (1987).
443. L. C. Morejohn, T. E. Bureau, L. P. Tocchi, and D. E. Fosket, *Planta* **170,** 230 (1987).
444. G. R. Donaldson, M. R. Atkinson, and A. W. Murray, *Biochem. Biophys. Res. Commun.* **31,** 104 (1968).
445. H. M. Niemeyer, N. B. Calcaterra, and O. A. Roveri, *Biochem. Pharmacol.* **35,** 3909 (1986).
446. F. J. Perez and H. M. Niemeyer, *Phytochemistry* **28,** 1597 (1989).
447. F. J. Perez and H. M. Niemeyer, *Phytochemistry* **28,** 1831 (1989).
448. L. Cuevas, H. M. Niemeyer, and F. J. Perez, *Phytochemistry* **29,** 1429 (1990).
449. M. T. Huang, *Mol. Pharmacol.* **11,** 511 (1975).
450. S. Remillard, L. I. Rebun, G. A. Howe, and S. M. Kupchan, *Science* **189,** 1002 (1975).
451. L. Carrasco, M. Fresno, and D. Vazquez, *FEBS Lett.* **52,** 236 (1975).
452. C. D. Howes, *Phytochemistry* **13,** 1469 (1974).
453. R. C. French and C. L. Wilson, *Physiol. Plant Pathol.* **19,** 201 (1981).
454. B. Gilbert, *Pontif. Acad. Sci. Scr. Varia* **10,** II(9), 225 (1977).
455. Y. Hafuri, E. Takemori, K. Oogose, Y. Inouye, S. Nakamura, Y. Kitahara, S. Nakahara, and A. Kubo, *J. Antibiot.* **41,** 1471 (1988).
456. W. A. Tramontano, C. M. Hartnett, D. G. Lynn, and L. S. Evans, *Phytochemistry* **21,** 1201 (1982).
457. D. G. Lynn, D. H. Lewis, W. A. Tramontano, and L. S. Evans, *Phytochemistry* **23,** 1225 (1984).
458. G. W. Arnold and J. I. Hill, *in* "Phytochemical Ecology" (J. B. Harborne, ed.), p. 92. Academic Press, New York, 1971.
459. H. J. Troll, *Züchter* **19,** 153 (1948/1949).
460. P. Cantot and J. Papineau, *Agronomie* **3,** 937 (1983).
461. M. Wink, T. Hartmann, L. Witte, and J. Rheinheimer, *Z. Naturforsch.* **37C,** 1081 (1982).
462. W. Wegorek, and J. Krzymanska, *Pr. Nauk Inst. Ochr. Rosl.* **13,** 7 (1971).
463. M. Rowell-Rahier and J. M. Pasteels, *J. Chem. Ecol.* **12,** 1189 (1986).
464. I. Forbes and E. W. Beck, *Agron. J.* **46,** 528 (1954).
465. M. Wink and P. Römer, *Naturwissenschaften* **73,** 210 (1986).
466. S. D. Cline and C. J. Coscia, *Plant Physiol.* **86,** 161 (1988).
467. S. D. Cline and C. J. Coscia, *Planta* **178,** 303 (1989).
468. U. Eilert and F. Constabel, *J. Plant Physiol.* **125,** 167 (1986).

469. U. Eilert, W. G. W. Kurz, and F. Constabel, *J. Plant Physiol.* **119,** 65 (1985).
470. H.-M. Schumacher, H. Gundlach, F. Fiedler, and M. H. Zenk, *Plant Cell Rep.* **6,** 410 (1987).
471. T. Tanahashi and M. H. Zenk, *Phytochemistry* **29,** 1113 (1990).
472. U. Eilert, F. Constabel, and W. G. W. Kurz, *J. Plant Physiol.* **126,** 11 (1986).
473. F. DiCosmo, A. Quesnel, M. Misawa, and S. G. Tallevi, *Appl. Biochem. Biotechnol.* **14,** 1010 (1987).
474. B. Wolters and U. Eilert, *Z. Naturforsch.* **37C,** 575 (1982).
475. U. Eilert, A. Ehmke, and B. Wolters, *Planta Med.* **6,** 508 (1984).
476. P. Heinstein, *J. Nat. Prod.* **48,** 1 (1985).
477. G. Krauss, G. J. Krauss, R. Baumbach, and D. Gröger, *Z. Naturforsch.* **44C,** 712 (1989).
478. P. M. Frischknecht and T. W. Baumann, *Phytochemistry* **24,** 2255 (1985).
479. I. T. Baldwin, *Oecologia* **75,** 376 (1988).
480. I. T. Baldwin, *Oecologia* **77,** 378 (1988).
481. M. B. Khan and J. B. Harborne, *Chemoecology* **1,** 77 (1990).
482. M. Wink, *Z. Naturforsch.* **38C,** 905 (1983).
483. M. Wink, *in* "Primary and Secondary Metabolism of Plant Cell Cultures" (K. H. Neumann, W. Barz, and E. Reinhard, eds.), p. 107. Springer-Verlag, Heidelberg, 1985.
484. M. Wink, *Planta Med.* **53,** 509 (1987).
485. M. Wink and L. Witte, *FEBS Lett.* **159,** 196 (1983).
486. M. Wink, H. J. Heinen, H. Vogt, and H. M. Schiebel, *Plant Cell Rep.* **3,** 230 (1984).
487. M. Wink, Habilitation-Thesis, Technische Universität Braunschweig, Germany, (1984).
488. M. Wink, L. Witte, and T. Hartmann, *Planta Med.* **43,** 342 (1981).
489. M. Wink, *Z. Naturforsch.* **41C,** 375 (1986).
490. M. Wink and T. Hartmann, *Z. Pflanzenphysiol.* **102,** 337 (1981).
491. M. Wink and L. Witte, *Planta* **161,** 519 (1984).
492. A. Szentesi and M. Wink, *J. Chem. Ecol.* **17,** 1557 (1991).
493. N. D. Johnson, L. Rigney, and B. L. Bentley, *J. Chem. Ecol.* **15,** 2425 (1989).
494. M. S. Blum, "Chemical Defenses of Arthropods." Academic Press, New York, 1981.
495. W. Fenical, *in* "Alkaloids: Chemical and Biological Perspectives" (S. W. Pelletier, ed.), Vol. 4, p. 276. Wiley, New York, 1986.
496. J. M. Pasteels and M. Rowell-Rahier, *Annu. Rev. Entomol.* **28,** 263 (1983).
497. H. Molisch, "Der Einfluss einer Pflanze auf die Andere- Allelopathie." Fischer, Jena, Germany, 1937.
498. C. H. Muller, *Rec. Adv. Phytochem.* **3,** 106 (1970).
499. A. R. Putman and C. S. Tang, "The Science of Allelopathy." Wiley, Chichester, 1986.
500. E. L. Rice, "Allelopathy," 2nd Ed. Academic Press, New York, 1984.
501. E. Kaissling, "R. H. Wright Lectures on Insect Olfaction." Simon Fraser Univ., Burnaby, British Columbia, 1987.
502. L. Roth, M. Daunderer, and K. Kormann, "Giftpflanzen, Pflanzengifte" 3rd Ed. Ecomed. Landsberg, Munich, 1984.
503. M. Wink, *in* "Focus on Insect–Plant Interactions" (E. Bernays, ed.), Vol. 4, p. 131. CRC Press, Boca Raton, 1992.
504. E. Stahl, *Jena. Z. Med. Naturwiss.* **23,** 557 (1888).
505. T. Robinson, "The Biochemistry of Alkaloids," 2nd Ed. Springer-Verlag, Heidelberg, New York, 1981.
506. G. R. Waller and E. Nowacki, "Alkaloid Biology and Metabolism in Plants." Plenum, New York, London, 1978.
507. E. A. Bernays and S. J. Simpson, *Adv. Insect Physiol.* **16,** 59 (1982).

508. L. B. Brattsten and S. Ahmad, "Molecular Aspects of Insect Plant Associations." Plenum, New York, 1986.
509. M. Wink, *in* "Methods of Plant Biochemistry," In press.
510. M. Wink, *in* "Secondary Products in Plant Tissue Culture" (B. V. Charlwood and M. J. C. Rhodes, eds.), Oxford Univ. Press (Clarendon), Oxford, 1990.
511. M. Wink and L. Witte, *Entomol. Gen.* **15,** 237, 1991.
512. M. T. Hauser and M. Wink, *Z. Naturforsch.* **45C,** 949 (1990).
513. K. Clay, *Annu. Rev. Ecol. Syst.* **21,** 275 (1990).
514. M. Wink, C. B. Montllor, E. A. Bernays, and L. Witte, *Z. Naturforsch.* **46C** 1080 (1991).
515. D. E. Dussourd, C. A. Harvis, J. Meinwald, and T. Eisner, *Experientia* **45,** 896 (1989).
516. D. E. Dussourd, K. Ubik, C. Harvis, J. Resch, J. Meinwald, and T. Eisner, *Proc. Natl. Acad. Sci. U.S.A.* **85,** 5992 (1988).
517. M. Wink and D. Schneider, *Naturwissenschaften* **75,** 524 (1988).
518. M. Wink and D. Schneider, *Z. Naturforsch.* **43C,** 737 (1988).
519. A. Egelhaaf, K. Cölln, B. Schmitz, M. Buck, M. Wink, and D. Schneider, *Z. Naturforsch.* **45C,** 115 (1990).
520. E. von Nickisch-Rosenegk, D. Schneider, and M. Wink, *Z. Naturforsch.* **45C,** 881 (1990).
521. M. Wink, E. von Nickisch-Rosenegk, and D. Schneider, *Symp. Biol. Hung.* **39,** 53 (1990).
522. T. Johns, *J. Chem. Ecol.* **12,** 635 (1986).
523. E. von Nickisch-Rosenegk and M. Wink, *J. Chem. Ecol.* In press.
524. A. Ehmke, M. Rowell-Rahier, J. M. Pastells, and T. Hartmann, *J. Chem. Ecol.* **17,** 2376 (1991).
525. J. Meinwald, *Pure Appl. Chem.* **62,** 1325 (1990).
526. W. O. James, *in* "The Alkaloids" (R. F. Manske, and H. L. Holmes, eds.), Vol. 1, p. 71. Academic Press, New York, 1950.
527. M. Wink, *ACS Symp. Ser.* **330,** 524 (1987).
528. J. P. Dumbadner, B. M. Beehler, T. F. Spande, H. M. Garraffo, and J. W. Daly, *Science* **258,** 799 (1992).
529. H. J. Preusser, *Toxicon* **13,** 114 (1975).