Evolution of the Angiosperms and Co-evolution of Secondary Metabolites, Especially of Alkaloids

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Contents

Abstract

Plants produce a wide variety of secondary metabolites (PSM) for protection against herbivores, microorganisms, and competing plants. PSM also function as signal compounds to attract pollinating and fruit-dispersing animals. PSM occur in complex mixtures, which vary between organs and developmental stages of a plant. PSM have been structurally optimized during evolution to affect molecular targets in animals, other plants, and microbes. Many insect herbivores have adapted to the defense chemistry of their host plants and are mono- and oligophagous. The largest class of PSM are alkaloids, which often function as strong neurotoxins against insects and vertebrates. Whereas the production of alkaloids is very limited in spore bearing plants and gymnosperms, they

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are dominant in angiosperms, which comprise more than 90% of all living plants. Angiosperms develop showy flowers to attract pollinators. However, these pollinators should only feed on nectar but not on the aerial parts or flowers of a plant. It is argued that the diversification of angiosperms was a driving force for the radiation and diversification of insects, which comprise the majority of animals with more than 1.4 million species. As a sort of co-evolution, angiosperms, which rely on animal pollination, started to produce a wide diversity of neurotoxic and fast-acting alkaloids to keep their animal visitors under control.

Keywords
Plant phylogeny · Secondary metabolites · Alkaloids · Co-evolution · Pollination · Herbivory · Chemical defense

Abbreviations

AMP	Antimicrobial peptide
PSM	Plant secondary metabolite

1 Introduction: Evolution and Functions of Secondary Metabolites

1.1 Plant Secondary Metabolism

A characteristic feature of plants is the production of low-molecular weight compounds, termed secondary metabolites (PSM) or natural products (Fig. 1) [1–10]. PSM are produced in specific biosynthetic pathways with the aid of substrate specific enzymes. The precursors of PSM derive from primary metabolites of plant metabolism, such as amino acids, sugars, fatty acids, or acetyl-CoA. Thus, primary and secondary metabolism are tightly connected [2, 11].

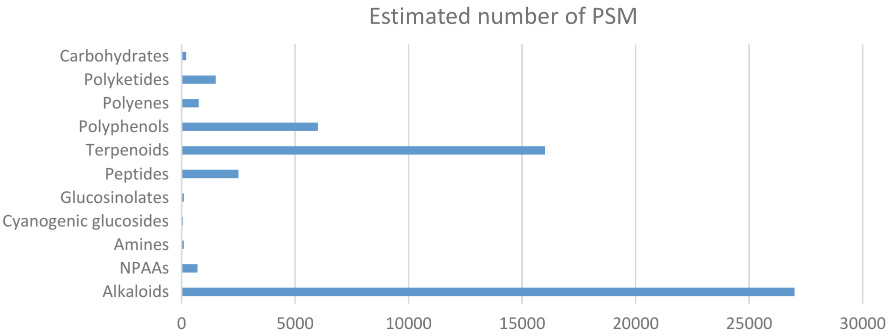

Fig. 1 Estimated number of PSM

Most PSM are stored in plants in relatively high concentrations, which can exceed more than 10% of total dry weight. Water-soluble PSM are usually stored in the vacuole of plant cells, often the epidermal cells. Lipophilic compounds are not sequestered in the vacuole but excreted into raisin ducts, lacticifers, oil cells, trichomes, dead cells, or the cuticle [5, 11, 12].

PSM can be synthesized in almost any plant organ, but this differs from plant species to another or types of PSM. Some plants produce a PSM in the root, but store it in the aerial parts (e.g., tropane alkaloids or *Nicotiana* alkaloids). In order to reach the aerial parts, PSM undergo long-distance transport via the xylem. Other plants produce PSM in the leaves, sometimes even in chloroplasts. If these PSM are accumulated in roots, stems, flowers, or seeds, they are usually transported there via the phloem (e.g., quinolizidine alkaloids) [11].

Plants usually do not produce a single PSM but a couple of main PSM and several derivatives, differing by additional hydroxyl, methoxy, epoxy, aldehyde, or ester moieties or the degree of oxidation. These additional functional groups can influence the biological activity of a PSM [13, 14]. In many instances, plants not only produce a mixture of PSM from the same class of PSM but from several classes. The composition of these mixtures differs between plant organs, i.e., PSM of roots differ from those of leaves or seeds. Furthermore, PSM profiles differ between developmental stages; i.e., profiles from seedlings differ from those of mature flowering or senescing plants [11]. This feature is important for our discussion of co-evolution of angiosperms and herbivores. Within a population, a substantial variation in content and composition of PSM can be expected. This variation can be due to genetic or environmental factors. Plants growing at a sunny site have a different PSM profile from those living in the shade, or mountain populations differ from low-land populations.

Most PSM are not end products but can undergo metabolism. Nitrogen--containing PSM are often used as nitrogen-storage compounds by some plants. Legumes (family Fabaceae), which store quinolizidine alkaloids, lectins, protease inhibitors, alkaloids, or nonprotein amino acids in their seeds, mobilize these PSM after germination and use their nitrogen for the developing young plant (Fig. 2). This feature is important, because nitrogen is a limiting factor for most plants and thus its use must be economic [2, 5, 11].

Plant secondary metabolism is not static. When plants are infected by a pathogen or wounded by an herbivore (an animals which feeds on plants), the secondary metabolism is often activated. Preformed PSMs are activated after cleavage of a sugar moiety by beta glucosidase or an esterase; examples are cyanogenic glucosides, glucosinolates, saponins, or flavonoid glycosides [15–17]. In other cases, the formation of existing PSMs is stimulated or in some plants completely new PSM are synthesized, mostly oriented against microorganisms. Plant pathologist have termed the new compounds “phytoalexins.” Plant hormones, such as gibberellic acid, jasmonic acid, salicylic acid, play important roles in the corresponding signal pathways (involving calcium signaling) and differential gene expression, which regulate plant responses to the environment [11, 15, 18].

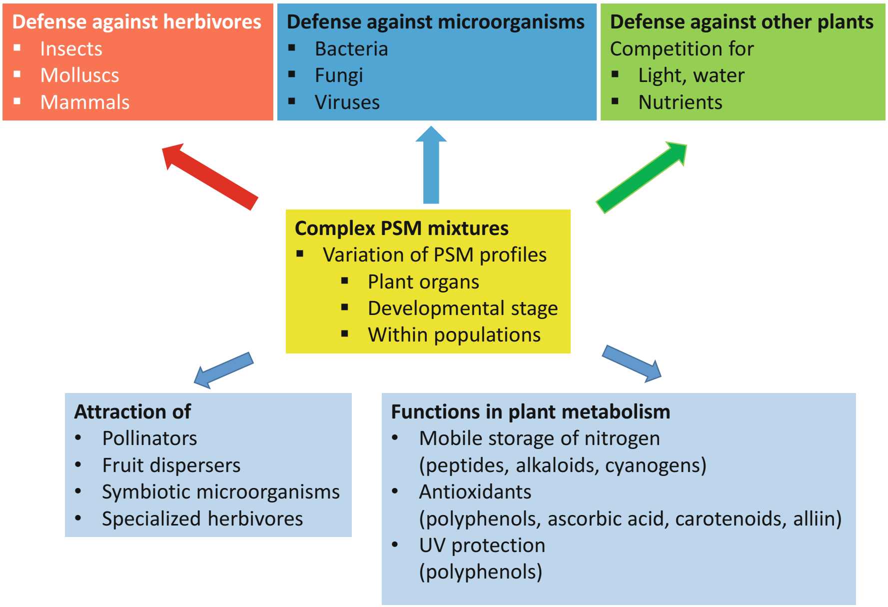

Fig. 2 Functions of PSM as defense, signal, or otherwise useful compounds

1.2 Functions of Plant Secondary Metabolites as Defense Compounds

During the last decades, it became more and more evident that PSM are not worthless waste products, but important for the survival and ecological fitness of a plant producing them [2, 5, 6, 11, 12, 15]. It is a trivial observation that plants cannot run away when they are attacked by an herbivore nor do they have an adaptive immune system (as animals have) to ward off microbial pathogens or parasites. The evolutionary solution of plants and often of other immobile organisms was the synthesis of defense compounds, which could interfere with the physiology, metabolism, or reproduction of potential enemies (Fig. 2). In common language, we would call such compounds toxins or antimicrobials. Thus, PSM, which we see today, have undergone several cycles of evolution screening by natural selection to make them biologically active. For this reason, many PSM or the herbs producing them can be used in pharmacy or medicine to treat infections and some health conditions [4, 16, 17]. I have thus termed the result of this process “evolutionary pharmacology” [14, 16, 17]. In conclusion, the main function of PSM mixtures is defense against herbivores (grazing mammals, insects, slugs, and mollusks). Plants also use mechanical features against herbivores, such as spines, thorns, stinging hairs, or a thick strongly textured bark. In addition, most plants have open growth and can replace plants parts, which have been damaged.

Sometimes, the same or other PSM are more directed against microorganisms and help to ward off bacteria, fungi and viruses, which are abundant in the environment. Antimicrobial PSM interfere with biomembranes of microbes (saponins, mono- and sesquiterpenes), of proteins (polyphenols), protein biosynthesis, and DNA replication and transcription (many alkaloids). In addition to antimicrobial PSM and antimicrobial peptides (AMPs), plants can block vessels by storing callose or can inhibit microbial infection by secreting chitinase, glucanase, and peroxidase [5, 11, 13–15].

Plants compete with other plants for light, water, and nutrients. In some instances, for example, in desert plants, a strong competition between plants of the same or different species can be observed, in a way that individual plants are surrounded by an empty space. It could be demonstrated that plants excrete PSM from their rhizosphere or from leaves, which can inhibit the germination or development of other competing plants. This phenomenon has been termed “allelopathy” (Fig. 2) [2, 5, 7, 19].

1.3 Functions of Plant Secondary Metabolites as Signal Compounds

It appears to be contradictory that plants also use PSM as signal compounds to attract pollinating insects, fruit-dispersing animals, or symbiotic root bacteria (Fig. 2). Mostly, we see the same PSM, which are employed in defense against herbivores. How to explain this contradiction? Flowering plants (angiosperms) produce conspicuous flowers to attract pollinators. Attraction is achieved via colors (mostly anthocyanins, some flavonoids, and carotenoids) which insect can perceive in normal but also UV light. In addition, many plants employ aromatic PSM (mostly terpenoids) as an additional olfactory attractants. Some plants produce foully smelling PSM, such as amines to attract flies and beetles [2, 5, 6, 19–21]. These strategies help to attract pollinators to the vicinity of a flower. But the pollinator should not feed on the flower itself, but instead is rewarded by nectar. Nectar is usually rich in sucrose or glucose and may contain some lipids and amino acids. In some plants, the nectar also sequesters PSM [22–24]. Thus, the PSM in flowers function as deterrent at low distance. In addition to insects (honey bees, solitary bees, bumblebees, pollen wasps, ants, flies, bee flies, hover flies, mosquitos, butterflies, moths, flower beetles), some plants (often with red flowers) employ birds (sugar birds, sun birds, humming birds, bats) as pollinators [2].

In contrast to plants which use animals (entomophilous and zoophilous species), the majority of gymnosperms and many angiosperms (taxa within Poales, such as grasses, sedges, and rushes; Fagaceae, Betalaceae, Junglandaceae, Vitaceae) use wind-pollination (anemophily). Anemophilous plants do not produce showy flowers, lack nectar but produce large amounts of pollen grains. As discussed later, wind-pollinated plants are often without strong poisons, such as alkaloids.

Some plants, which produce fruits, are interested that their seeds are dispersed away from the producing plants [3–5]. To achieve this purpose, plants produce fruits, which are attractive to fruit eating animals (frugivores), such as certain birds, primates, or bats. In this case, the seeds can withstand the digestive process and are discarded in the feces, usually at a different site. To be attractive, mature fruits are often rich in nutritive sugars and have an aromatic smell. As only mature fruits should be consumed, unripe fruits are often rich in bitter or acidic PSMs and do not advertise themselves by conspicuous colors, i.e., they are mostly green [11, 15].

Plants use some of their PSM in addition as mobile nitrogen storage compounds, as antioxidants or for UV defense (Fig. 2) [11, 15]. Thus, PSMs can have multiple purposes for the plants producing and storing them.

1.4 Adaptation of Herbivores

Whereas chemical defense works in most instances against most polyphagous herbivores, some monophagous herbivores have evolved a tolerance towards a particular toxin of its host plants. Some insects can quickly detoxify and eliminate dietary PSMs, a few other sequester these PSM and use them for their own defense against predators. These specialists can thus exploit a specific host plant without being poisoned. But they cannot feed on other unrelated plants [2, 20, 21, 25–30].

Special adaptations are required for this process, often involving several mutational steps. For example, larvae of the Monarch butterfly can feed on *Asclepias* plants, which produce cardiac glycosides which are poisonous for most animals. In the Monarch, a mutation of Na^+, K^+ -ATPase in the binding site for cardiac glycosides confers resistance. Larvae and adult Monarch butterflies become toxic themselves and are avoided by insectivorous birds [31–35]. Similar adaptations have been observed in insects, mostly in moths, butterflies, beetles, and bugs, and comprise several neurotoxic PSM, such as cardiac glycosides, pyrrolizidine alkaloids, quinolizidine alkaloids, cyanogenic glucosides, but also iridoid glucosides, glucosinolates, and polyphenols [2, 13, 21, 36–43]. In most instances, the exact molecular adaptations have not been discovered.

As a consequence of these adaptations, many insects are mono- and oligophagous.

2 Evolution and Function of Alkaloids

As mentioned above, plants produce a wide diversity of PSMs, which can be classified by their ring structures or biochemical pathways from which they derived (Fig. 1). Formally, we can distinguish between nitrogen-containing PSM and nitrogen-free PSM, such as terpenoids, phenolics and tannins, anthraquinones and polyenes. The class of PSM with nitrogen in their molecule is dominated by alkaloids, of which more than 27,000 structures have been described. In this class, we also find nonprotein amino acids (NPAA; more than 700 structures), glucosinolates (ca. 100 structures), cyanogenic glucosides (80 structures), and amines and several peptides [lectins, protease inhibitors, and antimicrobial peptides (AMPs)] [1, 3–5, 7, 8, 11, 16, 17, 44].

Whereas alkaloids are often powerful neurotoxins, NPAAs are mimics of the 20 proteinogenic amino acids and can be incorporated into proteins. These proteins show a wrong secondary and tertiary structure and thus are often functionless. Thus, NPAAs function as metabolic disruptors [14, 16, 17, 21, 44]. When cyanogenic glucosides are hydrolyzed, they release HCN, which is a powerful inhibitor of the respiratory chain in mitochondria and thus inhibits the formation of ATP. They are thus powerful metabolic poisons [2, 4, 21]. When glucosinolates are cleaved, lipophilic mustard oils or isothiocyanates are liberated. They disturb membrane fluidity, bind to proteins and DNA bases, and cause inflammation, a pungent taste, and pain [14, 16, 17]. Lectins often interfere with ribosomal protein biosynthesis, protease inhibitors inhibit proteases of the digestion process, and AMPs influence membrane fluidity and stability in microbial and eukaryotic cells.

Alkaloids contain one or several nitrogen atoms, mostly in their ring structures. They form a free base under alkaline conditions and are charged molecules below pH 7 (i.e., in most plants and in target organisms, alkaloids are mostly present in a protonated form). However, when we draw them, we usually show the free base.

Depending on the biosynthetic pathways and ring structures, alkaloids are divided into the following groups: pyridine, pyrimidine, pyrrol, piperidine, pyrrolizidine, quinolizidine, indolizidine, isoquinoline, quinoline, indol, monoterpene indole, terpenoid, and steroidal alkaloids. The main amino acids, which serve as precursors, are phenylalanine/tyrosine (isoquinoline alkaloids, including protoberberine and morphinane alkaloids), tryptophan (indol alkaloids, monoterpene indole alkaloids, and quinoline alkaloids), lysine (piperidine and quinolizidine alkaloids), ornithine/arginine (tropane and pyrrolizidine alkaloids) [45–51].

As mentioned above, alkaloids often function as neurotoxins, others are cytotoxic, as they interfere with biomembranes, microtubules, actin filaments, enzymes, and DNA/RNA and corresponding enzymes [5, 6, 15, 44, 45, 47, 51–54]. In case of neurotoxic alkaloids, they often mimic the structure of neurotransmitters, such as acetylcholine, noradrenaline, adrenaline, serotonin, dopamine, or endorphins (Table 1). They can either block the neurotransmitter receptor as antagonist or stimulate it as agonist. Some alkaloids inhibit the activity of enzymes, which degrade neurotransmitters, such as acetylcholine esterase or monoamine oxidase (MAO). Also, the uptake protein for neurotransmitters into the presynapse or the neurovesicles can be inhibited. Several toxic alkaloids inhibit or activate ion channels (Na^+, K^+, Ca^{++}) or Na^+, K^+-ATPase [14, 16, 17, 43, 44, 48, 53–55]. Some alkaloids have a single target, many others and the majority of PSM are multitarget compounds, which are directed against several targets in animals and/or microorganisms. In conclusion, most alkaloids are known for their pronounced toxicological properties and some of them are lethal poisons others are used in medicine to treat health conditions [14, 16, 17]. From a plants point of view, alkaloids are mostly employed as defense compounds against herbivores and many of the alkaloid-accumulating plants are avoided by herbivores.

Table 1 Interaction of some alkaloids with neuroreceptors and other elements of neuronal signaling. (Source: Refs. [51, 53])

Target	Natural ligand/ substrate	Alkaloid	Occurrence
Acetylcholine receptor			
Nicotinic receptor	Acetylcholine	Nicotine	*Nicotiana, Duboisia*
		C-toxiferine	*Strychnos*
		Tubocurarine	*Chondrodendron*
		Coniine	*Conium*
		Cytisine and other QAs	Several Fabaceae
		Lobeline	*Lobelia*
		Anabasine	*Anabasis, Nicotiana*
Muscarinic receptor	Acetylcholine	Hyoscyamine (atropine)	*Atropa, Hyoscyamus, Datura, Mandragora*
		Scopolamine	Several Solanaceae
		Arecoline	*Areca*
		Pilocarpine	*Pilocarpus*
		Muscarine	*Amanita, Clitocybe,* other fungi
		Sparteine and other QAs	Several Fabaceae
Adrenergic receptors	Noradrenaline/ adrenaline	Ergot alkaloids	*Claviceps*
		Yohimbine	*Pausinystalia, Aspidosperma*
		Rauwolscine	*Rauvolfia*
		Corynanthine	*Rauvolfia*
		Norlaudanosollne	Papaveraceae
		Ephedrine, norephedrine	*Ephedra, Catha*
Dopamine receptor	Dopamine	Ergot alkaloids	*Claviceps*
		Bulbocapnine	*Corydalis*
Serotonin receptor	Serotonin	Ergot alkaloids	*Claviceps*
		Psilocin, psilocybin	*Psilocybe,* other fungi
		N,*N*-dimethyltryptamine	Several plants and toads
		Bufotenine	*Virola, Anadenanthera*
		Beta-carboline alkaloids	*Banisteriopsis, Peganum*
		Mescaline	*Lophophora, other cacti*

(*continued*)

Table 1 (continued)

Target	Natural ligand/ substrate	Alkaloid	Occurrence
GABA receptor	Gamma aminobutyric acid (GABA)	Bicuculline	*Dicentra cucullaria, Corydalis,*
		Muscimol	*Amanita*
		Beta-carboline alkaloids	*Peganum, Banisteriopsis*
Adenosine receptor	Adenosine	Caffeine	*Coffea, Camellia, Ilex, Paullinia*
		Theophylline, Theobromine	*Theobroma*
Glycine receptor	Glycine	Brucine	*Strychnos*
		Strychnine	*Strychnos*
Opioid receptor	Endorphins	Morphine	*Papaver somniferum*
Acetylcholine esterase	Acetylcholine	Physostigmine (eserine)	*Physostigma venenosum*
		Berberine	Several Papaveraceae
		Coptisine	Several Papaveraceae
		Galantamine	Several Amaryllidaceae
		Solanine and other steroid alkaloids	*Solanum*
		Huperzine A	*Huperzia serrata*
Monoamine oxidase (MAO)	Noradrenaline, dopamine, serotonin, histamine	Harmaline, harmine	*Peganum*
		Salsolinol	Chenopodiaceae
Catechol-*O*-methyltransferase	Noradrenaline, adrenaline, dopamine	Tetrahydroisoquinoline	Papaveraceae
Na$^+$/K$^+$ channels	Na$^+$, K$^+$	Aconitine	*Aconitum*
		Quinidine	*Cinchona*
		Sparteine, lupanine	*Lupinus, Cytisus*
		Protoveratrine A	*Veratrum*

2.1 Evolution of Alkaloids

When were PSM invented during evolution? For our discussion, Fig. 3 illustrates a molecular phylogeny of plants, which is based on DNA sequences and transcriptome analyses [56, 57]. From a global perspective, we can state that already the early land plants needed chemical defense against herbivores and microbes as these organisms already existed when land plants evolved in the Devonian. Widely present in extant spore-bearing plants, gymnosperms and angiosperms are terpenoids and polyphenols. It can be speculated that these PSMs already evolved more than 500 million years ago.

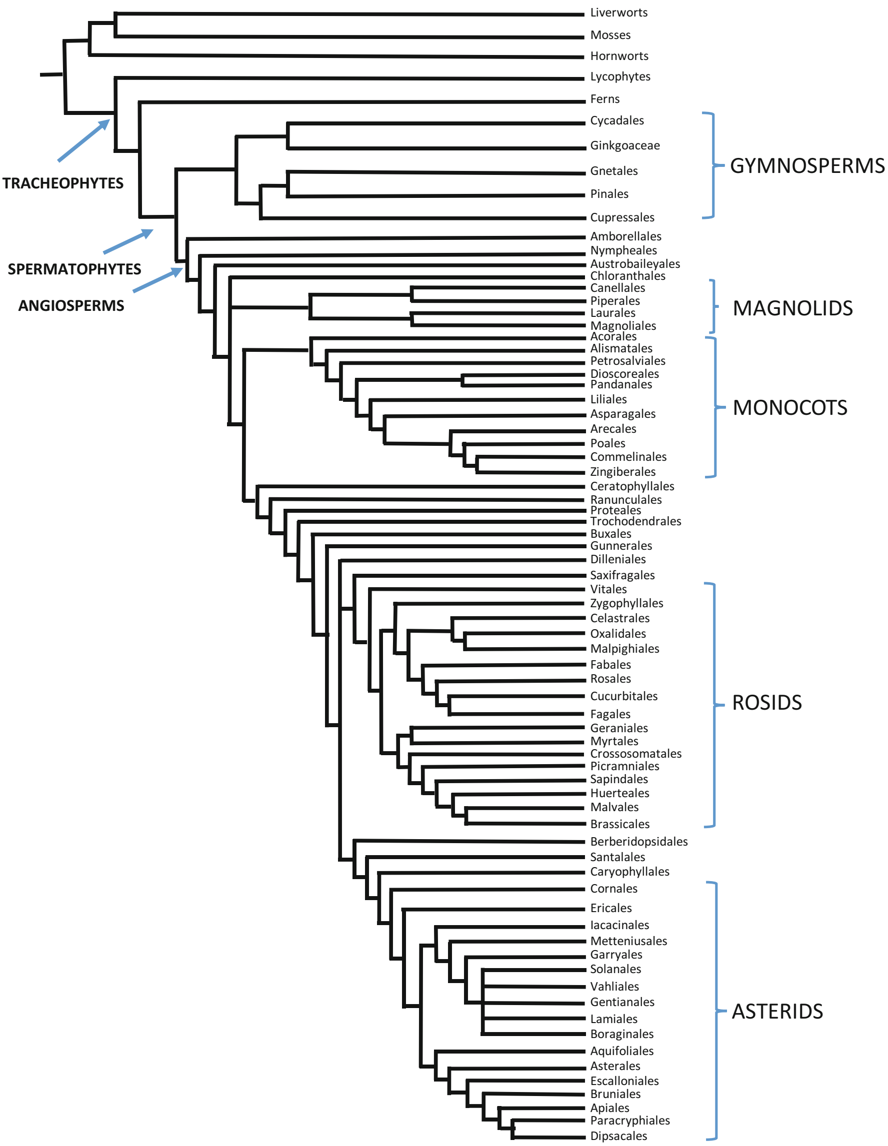

Fig. 3 Phylogeny reconstruction of plants according to APGIII and One Thousand Plant Transcriptomes Initiative [57]

Genes of corresponding biosynthetic pathways exist in all plants and algae and even in many microorganisms, suggesting that these pathways are very old [5, 7, 8, 58].

What about alkaloids? Alkaloids are common among angiosperms, but much more restricted in gymnosperms and spore bearing plants (Table 2; Fig. 4). Among spore bearing plants (mosses, lycopods, ferns, horsetails), only lycopods commonly

Table 2 Occurrences of selected alkaloids among plants. (Source: Refs: [3, 9, 60])

Alkaloid type	Example	Order	Family	Genus (selection)
Amaryllidaceae alkaloids	Ambelline, brunsvigine, galanthamine, haemanthamine, lycorine	Asparagales	Amaryllidaceae	*Amaryllis*, *Ammocharis*, *Boophane*, *Brunsvigia*, *Clivia*, *Crinum*, *Galanthus*, *Haemanthus*, *Hippeastrum*, *Hymenocallis*, *Leucojum*, *Lycoris*, *Narcissus*, *Nerine*, *Pancratium*, *Sternbergia*, *Ungermia*, *Zephyranthes*
Betalain alkaloids	Amaranthin, betanin, miraxanthin, vulgaxanthin-I	Caryophyllales	Aizoaceae, Amaranthaceae/ Chenopodiaceae, Cactaceae, Nyctaginaceae, Phytolaccaceae, Portulacaceae	*Amaranthus*, *Atriplex*, *Beta*, *Bougainvillea*, *Celosia*, *Chenopodium*, *Gomphrena*, *Mesembryanthemum*, *Mirabilis*, *Opuntia*, *Portulaca*, *Phytolacca*
Diterpenoid alkaloids	Aconitine, delphinine, delsonine, lycaconithine, lycoctonine, spiradine A	Ranunculales	Ranunculaceae	*Aconitum*, *Atragene*, *Consolida*, *Delphinium*, *Thalictrum*
	Anopterine	Saxifragales	Saxifragaceae	*Anopterus*
	Cassaine	Fabales	Fabaceae	*Erythrophleum*
	Cuauchichine, garryine, lindheimerine,	Garryales	Garryaceae	*Garrya*
	Icaceine	Icacinales	Iacacinaceae	*Icacina*
	Ryanodine	Malpighiales	Salicaceae	*Ryania*
	Spiradine A	Rosales	Rosaceae	*Spirea*
Indole alkaloids	Ajmalicine, ajmaline, akuammidine, alstonine, brucine, calebassine, catharanthine, C-curarine, eburnamine, ellipticine, gelsemine, ibogaine, mitragynine, reserpine, rutaecarpine, sempervirine, serpentine, strychnine, tabernamine,	Gentianales	Apocynaceae, Loganiaceae, Rubiaceae	*Adina*, *Alstonia*, *Amsonia*, *Aspidosperma*, *Borreria*, *Catharanthus*, *Cephaelis*, *Cinchona*, *Corynanthe*, *Evodia*, *Geissospermum*, *Gelsemium*, *Flindersia*, *Hortia*, *Hunteria*, *Melodinus*, *Mitragyna*, *Murraya*,

(continued)

Table 2 (continued)

Alkaloid type	Example	Order	Family	Genus (selection)
	tabersonine, toxiferine-I, vinblastine, vincamine, yohimbine			*Ochrosia*, *Pausinystalia*, *Picralima*, *Rauwolfia*, *Rhazya*, *Strychnos*, *Tabernaemontana*, *Uncaria*, *Vallesia*, *Vinca*, *Voacanga*, *Zanthoxylum*
	Agroclavine, chanoclavine-I, ergine	Solanales	Convolvulaceae	*Ipomoea*, *Rivea*
	Canthinone, 11-hydroxycanthin-6-one	Sapindales	Simaroubaceae	*Amaroria*, *Picrasma*, *Quassia*
	Eseramine, physostigmine	Fabales	Fabaceae	*Physostigma*
	Harmaline, harman	Zygophyllales	Zygophyllaceae	*Peganum*, *Zygophyllum*
	Harmaline	Malpighiales	Malpighiaceae	*Banisteriopsis*
	Mesembrine	Caryophyllales	Aizoaceae	*Sceletium*
Isoquinoline alkaloids	Actinodaphnine, atherospermoline, bebeerine, berbamine, boldine, glaucine, laudanidine, obaberine, reticuline	Laurales	Atherospermaceae, Hernandiaceae, Lauraceae, Monimiaceae	*Actinodaphne*, *Albertisia*, *Atherosperma*, *Beilschmidia*, *Boldea*, *Cassytha*, *Cryptocarpa*, *Daphnandra*, *Doryphora*, *Gyrocarpus*, *Hernandia*, *Larus*, *Laurelia*, *Litsea*, *Machilus*, *Monimia*, *Nectandra*, *Ocotea*, *Peumus*, *Phoebe*, *Sassafras*
	Adlumine, aknadicine, alpinine, argemonine, bebeerine, berberine, bicuculline, bulbocapnine, canadine, codeine, glaucine, hernandezine, jatrorrhizine, macarpine, magnoflorine, morphine, narceine, noscapine, palmatine, papaverine, reticuline, sanguinarine, tetrandrine, thalicarpine, thebaine, tubocurarine	Ranunculales	Berberidaceae, Menispermaceae, Papaveraceae, Ranunculaceae	*Abuta*, *Aconitum*, *Adlumia*, *Anisocycla*, *Argemone*, *Berberis*, *Bocconia*, *Chelidonium*, *Chondodendron*, *Cissampelos*, *Cocculus*, *Coptis*, *Corydalis*, *Dicentra*, *Dicranostigma*, *Eschscholzia*, *Glaucium*, *Hydrastis*, *Jateorrhiza*, *Leontice*, *Macleaya*, *Mahonia*, *Meconopsis*, *Menispermum*, *Nandina*, *Papaver*,

				Pycnarrhenia, *Romneya*, *Sanguinaria*, *Sinomenium*, *Stephania*, *Stylophorum*, *Thalictrum*, *Tiliacora*, *Zanthorrhiza*
	Alamarine, alangicine, ankorine, psychotrine	Cornales	Alangiaceae	*Alangia*
	Ancistrocladine, carnegine, gigantine, pellotine, pilocereine, salsoline	Caryophyllales	Ancistrocladaceae, Cactaceae, Chenopodiaceae	*Ancistrocladus*, *Carnegia*, *Cephalocereus*, *Cereus*, *Lophocereus*, *Lophophora*, *Pachycereus*, *Salsola*
	Angoline, berberine, canadine, dihydrosanguinarine, fagaridine, magnoflorine, sanguinarine	Sapindales	Rutaceae, Sapindaceae	*Evodia*, *Fagara*, *Pteridophyllum* *Toddalia*, *Zanthoxylum*
	Annolobine, berberine, boldine, jatrorrhizine, laudanidine, liriodenine, magnoflorine	Magnoliales	Annonaceae, Magnoliaceae	*Annona*, *Arbabotrys*, *Asimia*, *Coelocline*, *Desmos*, *Isolona*, *Liriodendron*, *Magnolia*, *Michelia*, *Phaeanthus*, *Xylopia*
	Annonaine	Nympheales	Nymphaceae	*Nelumbo*
	Bebeerine	Buxales	Buxaceae	*Buxus*
	Boldine	Rosales	Rhamnaceae	*Retanilla,*
	Caaverine	Ericales	Symplocaceae	*Symplocos*
	Cephaeline, emetine, papaverine, psychotrine	Gentianales	Apocynaceae, Rubiaceae	*Cephaelis*, *Rauwolfia*
	Cephaeline	Cornales	Cornaceae	*Alangium*
	Erythratidine, erythroidine	Fabales	Fabaceae	*Erythrina*
	Aristolochic acid, magnoflorine	Piperales	Aristolochiaceae	*Arstolochia*
	Pronuciferine	Proteales	Nelumbonaceae	*Nelumbo*
	Salutaridine	Malpighiales	Euphorbiaceae	*Croton*
	Colchicine	Liliales	Colchicaceae	*Colchicum*

(*continued*)

Table 2 (continued)

Alkaloid type	Example	Order	Family	Genus (selection)
Lycopodium alkaloids	Annotidine, cernuine, lycopodine, obscurine, selagine	Lycopodiales	Lycopodiaceae	*Lycopodium*
Pyrrolidine and piperidine alkaloids	Adenocarpine, ammodendrine, australine, cassine, castanospermine, juliflorine, pelletierine, santiaguine, swainsonine	Fabales	Fabaceae	*Adenocarpus*, *Ammodendron*, *Cassia*, *Castanospermum*, *Lupinus*, *Prosopis*, *Sophora*, *Swainsonia*
	Anabasine, anaferine, hygrine, myosmine, nicotine, nornicotine, pelletierine	Solanales	Convolvulaceae, Solanaceae	*Atropa*, *Convolvulus*, *Duboisia*, *Nicotiana*, *Withania*
	Anabasine	Caryophyllales	Chenopodiaceae	*Anabasis*
	Anabasine, lobeline	Asterales	Asteraceae, Campanulaceae	*Campanula*, *Lobelia*, *Zollikoferia*
	Anabasine	Cornales	Cornaceae	*Alangium*
	Arecaidine, arecoline	Arecales	Arecaceae	*Areca*
	Astrocasine, astrophylline, ricinine	Malpighiales	Euphorbiaceae	*Astrocasia*, *Ricinus*
	Carpaine, hygrine	Brassicales	Brassicaceae, Carcicaceae	*Carica*, *Cochlearia*, *Vasconcellea*
	Coniine, coniceine	Apiales	Apiaceae	*Conium*
	Hygrine	Asparagales	Orchidaceae	*Dendrobium*
	Pelletierine	Myrtales	Lythraceae	*Punica*
	Pelletierine, sedamine	Saxifragales	Crassulaceae	*Sedum*
	Pinidine	Pinales	Pinaceae	*Pinus*
	Piperine	Piperales	Piperaceae	*Piper*
Pyrrolizidine alkaloids	Anacrotine, fulvine, monocrotaline, platyphylline, retronecine, retrorsine, riddeline, seneciphylline, senkirkine	Fabales	Fabaceae	*Adenostyles*, *Crotalaria*, *Lotononis*
	Amabiline, clivorine, echimidine, europine, heliosupine, heliotrine, indicine, integerrimine, intermedine,	Boraginales	Boraginaceae	*Alkanna*, *Amsinckia*, *Anchusa*, *Borago*, *Cynoglossum*, *Echium*, *Heliotropium*, *Lappula*, *Lindelofia*,

	lasiocarpine, lycopsamine, monocrotaline, retronecine, rinderine, supinine, symphytine			*Messerschmidia*, *Myosotis*, *Rindera*, *Solenanthus*, *Symphytum*, *Tournefortia*, *Trichodesma*
	Auriculine	Asparagales	Orchidaceae	*Liparis*
	Angularine, clivorine, doronine, integerrimine, intermedine, jacobine, lycopsamine, petasitenine, platyphylline, retronecine, retrorsine, riddeline, rinderine, senecionine, seneciphylline, senkirkine, supinine	Asterales	Asteraceae	*Brachyglottis*, *Cacalia*, *Conoclinum*, *Doronicum*, *Emilia*, *Eupatorium*, *Farfugium*, *Ligularia*, *Petasites*, *Senecio, Tussilago*
	Lycopsamine	Gentianales	Apocynaceae	*Parsonsia*
Quinoline alkaloids	Acronidine, acronycine, arborine, bucharaine, dictamnine, evoxine, fagarine, graveoline, kokusaginine, maculine, melicopine, pteleatine, rutacridone, skimmianine	Sapindales	Rutaceae	*Acronychia*, *Adiscanthus*, *Aegle*, *Afraele*, *Atalantia*, *Balfourodendron*, *Bauerella*, *Cusparia*, *Dictamnus*, *Esenbeckia*, *Euodia*, *Fagra*, *Flindersia*, *Galipea*, *Glycosmis*, *Haplophyllum*, *Helietta*, *Lunasia*, *Melicope*, *Monnieria*, *Murraya*, *Orixa*, *Ptelea*, *Ruta*, *Sarcomelicope*, *Skimmia*, *Teclea*, *Zanthoxylum*
	Aniflorine, anisotine, peganine, vasicinol, vasicinone	Lamiales	Acanthaceae	*Adhatoda*, *Anisotes*
	Camptothecin, febrifugine	Cornales	Nyssaceae, Hydrangeaceae	*Camptotheca*, *Dichroa*, *Hydrangea*
	Camptothecin,	Icacinales	Icacinaceae	*Mappia*
	Camptothecin, Cinchonidine, quinine	Gentianales	Rubiaceae	*Cinchona*, *Ophiorrhiza*, *Remijia*
	Echinopsine	Asterales	Asteraceae	*Echinops*
	Peganine, vasicinone	Zygophyllales	Zygophyllaceae	*Nitraria*, *Peganum*
Quinolizidine alkaloids	Anagyrine, aloperine, ammonthamnine, angustifoline, aphylline, baptifoline, methylcytisine, cytisine, 13-	Fabales	Fabaceae	*Ammodendron*, *Ammothamnus*, *Anagyris*, *Argyrolobium, Baptisia*, *Cadia*, *Alpurnia*, *Cytisus*, *Euchresta*, *Genista*, *Goebelia*, *Hovea*,

(*continued*)

Table 2 (continued)

Alkaloid type	Example	Order	Family	Genus (selection)
	hydroxylupanine, lupanine, lupinine, matrine, multiflorine, ormosanine, piptanthine, retamine, sparteine, thermopsine			*Laburnum*, *Lamprolobium*, *Lupinus*, *Ormosia*, *Piptanthus*, *Retama*, *Podopetalum*, *Sophora*, *Spartium*, *Templetonia*, *Thermopsis*, *Ulex*, *Vexibia*
	Aphylline, lupinine	Caryophyllales	Chenopodiaceae	*Anabasis*
	Baptifoline, leontiformine	Ranunculales	Berberidaceae	*Caulophyllum*, *Leontice*
Steroidal alkaloids	Buxamine, cyclobuxine, terminaline	Buxales	Buxaceae	*Buxus*, *Pachysandra*
	Chaconine, demissine, solamargine, solanidine, solanine, solasonine, tomatidine	Solanales	Solanaceae	*Solanum*
	Chaconine, cyclopamine, germine, jervine, protoveratrine A and B, veracevine, verticine, zygadenine	Liliales	Liliaceae, Melianthaceae	*Fritillaria*, *Notholiron*, *Schoenocaulon*, *Veratrum*, *Zigadenus*
	Conessine, funtumine, paravallarine	Gentianales	Apocynaceae	*Funtumia, Holarrhena*, *Kibatalia*, *Paravallaris*
Tropane alkaloids	Atropine, convolamine, convolvine, hyoscyamine, littorrine, meteloidine, scopolamine, tigloidine	Solanales	Convolvulaceae, Solanaceae	*Anthocercis*, *Atropa*, *Datura*, *Duboisia*, *Hyoscyamus*, *Scopolia*, *Solandra*
	Benzylecgonine, cinnamoylcocaine, cocaine, ecgonine, meteloidine	Malpighiales	Erythroxylaceae	*Erythroxylum*
Cephalotaxus alkaloids	Cephalotaxine, harringtonine	Pinales	Cephalotaxaceae	*Cephalotaxus*
Equietum alkaloids	Palustrine	Equisetales	Equisetaceae	*Equisetum*
Taxus alkaloids	Paclitaxel (taxol), taxine A	Pinales	Taxaceae	*Taxus*

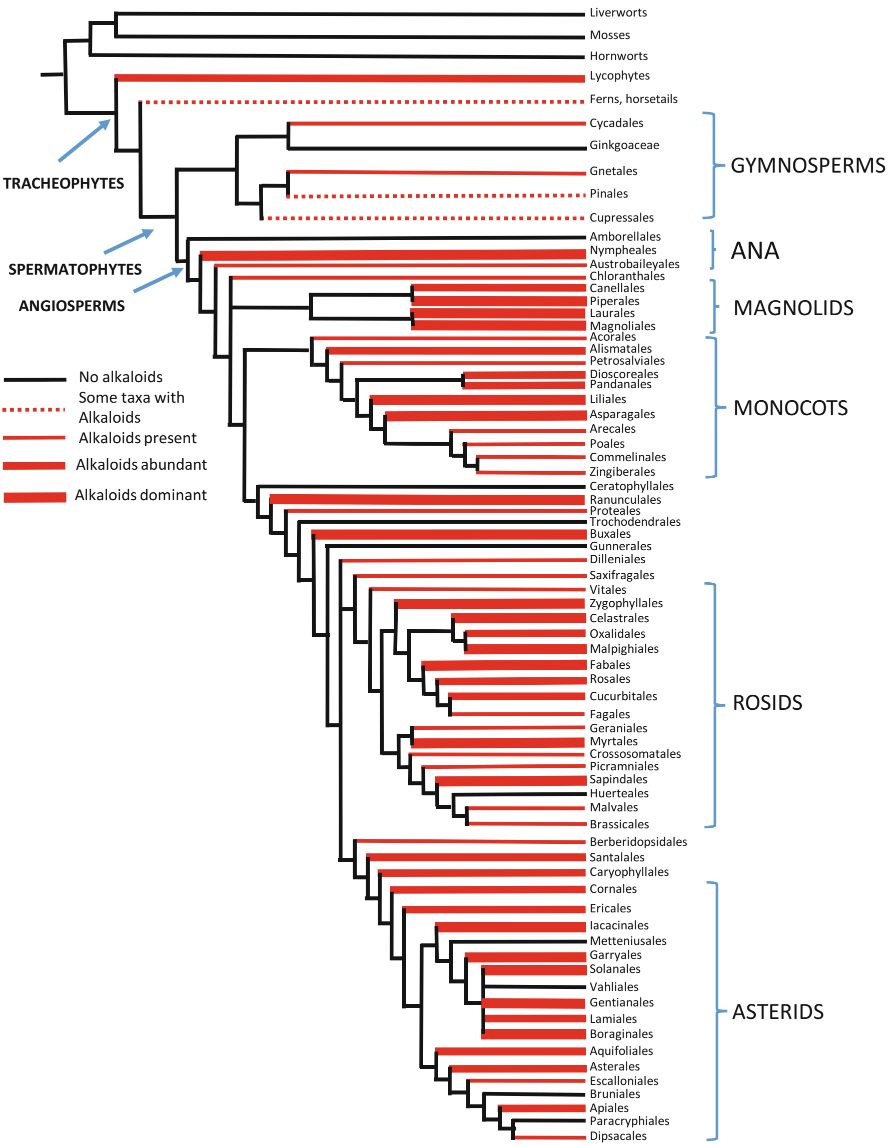

Fig. 4 Distribution of alkaloids in the plant kingdom

produce alkaloids of the quinolizidine type, where alkaloids are rare or absent in ferns, horsetails (except the alkaloid palustrine), and mosses [3–5, 59].

Among gymnosperms, cycads produce cycasin as an alkaloid, and the Ephedraceae the simple alkaloid ephedrine (and derivatives). Among plants of the orders Pinales and Cupressales, alkaloids are rarely produced in a few genera (Table 2) [3–5, 59].

Among angiosperms, some orders have more families producing alkaloids, than others (Fig. 4): Alkaloid-rich are Nympheales, Piperales, Magnoliales, Laurales, Liliales, Ranunculales, Buxales, Zygophyllales, Malpighiales, Fabales, Sapindales, Solanales, Gentianales, and Boraginales [3–5, 46, 47, 59].

Some types of alkaloids occur in closely related taxa (Table 2), which was the base for chemotaxonomy some time ago [59–63]. But a closer look shows that this feature is not consistent. For example, quinolizidine alkaloids occur predominantly in the tribe Genisteae of Fabaceae. But alkaloids with identical structures have also been detected in unrelated orders/families, such as Chenopodiaceae or Ranunculaceae. Or pyrrolizidine alkaloids occur in Boraginaceae, the tribe Crotalarieae of Fabaceae, and in the tribe Senecioneae of Asteraceae, which are unrelated families. Similar examples can be found for tropane, indole, and isoquinoline alkaloids (Table 2) [6–9, 15]. How to explain the irregular occurrences? It could be argued that the occurrence of a PSM in unrelated families is due to convergent evolution. Although convergence cannot be ruled out in all instances, genetic data favor a different hypothesis. When genomes of different plants and microorganisms were analyzed for the presence/absence of key enzymes of PSM biosynthesis, it turned out that the key enzymes are widely distributed in the plant kingdom, irrespective of whether a particular species produces a particular PSM or not. We have therefore postulated that the key genes of PSM biosynthesis are present in most if not in all plants and that the PSM profile observed in a particular plant is a consequence of differential gene expression. Furthermore, the origin of the key genes may be found in microorganisms, which also are active producers of secondary metabolites. These microbial genes probably entered plant genomes by horizontal gene transfer. According to the endosymbiont theory, plants have mitochondria, which derived from alpha Protobacteria and chloroplasts, which came from Cyanobacteria. The originally microbial genomes were incorporated into plant genomes, which thus obtained many genes which could be used later for the biosynthesis of PSM [7–9, 59, 64].

3 Evolution of Angiosperms, Pollinating Insects, and Defense via Alkaloids

First land plants occurred around 420 million years ago in the Silurian and became more common in the Devonian 416–359 million years ago. Fossils from this period mainly show plants which produced spores and resembled ferns (Psilophytatae). Later in the Devonian, tree-like lycopods, ferns, and horsetails followed which formed dense forests in the Devonian and Carbon (a source of our coal today). Starting in the Carboniferous, first gymnosperms occurred with cycads and gingko. Gymnosperms were abundant in Perm and the following Mesozoicum. About 140 million years ago in the Cretaceous, the largest group of plants, the angiosperms evolved and became the dominant flora, especially in the Palaeogene. Roots of most angiosperm orders go back to 100–120 million years ago. However, radiation and diversification within extant plant families occurred during the last 50 million years ago (Fig. 3) [58, 65].

The numbers of known plants is increasing over the years as new species are constantly being discovered: For our discussion, we only need to consider the actual numbers (not speculating on the unknown numbers of undescribed taxa): Species numbers: Bryophyta: 20,000; Pteridophyta: 13,000; Gymnosperms: 1100 and Angiosperms: 369,000 (Fig. 5a) [58, 65, 66].

Spore-bearing plants reproduce without the aid of animals. Also, most gymnosperms are wind-pollinated. Only cycads and Ephedra are visited by insects, which help to pollinate. In cycads, insects are mostly beetles and not flies and hymenopterans as in angiosperms.

The key innovation of angiosperms was the formation conspicuous flowers, with animals playing a role in pollination, whereas wind-pollinated angiosperms have inconspicuous flowers, such as in grasses. Flowers evolved in a way to attract animals for pollination. As already discussed above, flowers accumulate aromatic and colored PSM, such as anthocyanins, flavonoids, and carotenoids, which can be detected by insects and birds (nectar specialists, such as humming birds, sun birds). In some flowers, coloration (sometimes only visible in UV light) leads to the nectar source, which is the reward for the pollinating organism. The nectar of some plants contains bitter-tasting PSM, such as alkaloids [22, 23]. There is evidence that these PSMs provide a niche for some pollinators, which are adapted to the bitter-tasting PSM. An example is Anna's Hummingbird [24]. In this case, the nectar of a particular species is exclusive for a few pollinators, which may be of benefit for the plants, as this improved the likelihood that pollen of the same species is transferred by a pollinator.

In addition, many flowers produce aromatic and foully smelling fragrances, which are attractive for many insects (flies, bees, bumble bees, syrphid flies, butterflies). In some plants, these fragrances are mainly produced at night when certain kind of moth roam around for pollination [2, 21].

4 Co-evolution of Angiosperms, Animals, and Alkaloids

Among animals, chordates (which include mammals, birds, reptiles) consist of about 65,000 species in contrast to more than 1,360,000 species of invertebrates (Fig. 5b). The largest group within the invertebrates are insects with over one million species. Species numbers are uneven within insects: The major groups are Coleoptera (beetles) with 360,000–400,000 species, followed by Lepidoptera (moths and butterflies) with 175,000 species, Diptera (flies) with 153,000 species, Hymenoptera (bees, wasps, ants) with 115,000 species, and Hemiptera (aphids, bugs) with 88,000 species [58, 66]. A common theme for the species-rich insect groups is that many are pollinators and feed on plants at least in one developmental stage (e.g., as larvae many butterflies are herbivores and nectar feeders as adults).

It has been argued that the large number of insects is a consequence of the diversification of angiosperms, which constitute more than 94% of all vascular

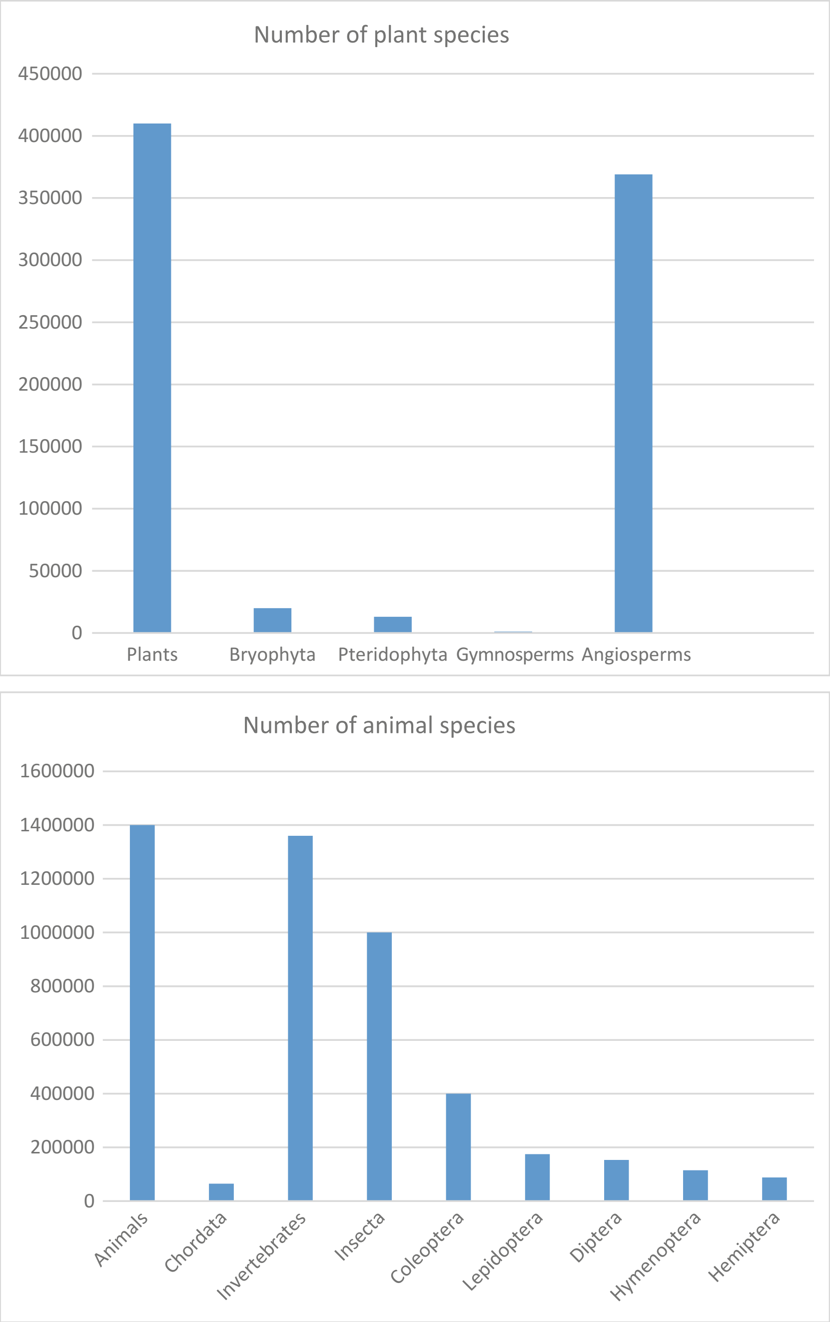

Fig. 5 Number of known plant (**a**) and animal (**b**) species

plants (Pteridophytes, Gymnosperms, Angiosperms) (Fig. 5a). A common theme for the largest groups of invertebrates is that they either feed on plants and/or that they are pollinators [19, 21, 67, 68]. Many insects are monophagous or oligophagous, meaning that they have specialized on one or a few host plants [21]. There is an estimate that a single plant species can be a host for more than 10 insect species. (In the biodiversity crisis, which we see today, a dramatic loss of insects has been recorded. This appears to be due to the increased application of insecticides in agriculture. In addition, the loss of plant diversity due to herbicides and over fertilization needs to considered. If we destroy the diversity of plants, we also destroy a food source for all the adapted herbivores.)

Why are there so many mono- and oligophagous insects? As discussed before, plants produce a wide diversity of PSM with deterrent and toxic properties, whose composition differs between plant parts and developmental stages (Fig. 2). Many insects nevertheless evolved strategies to feed on chemically defended plants or more precise a particular organ, by acquiring tolerance against the respective PSMs. If a PSM is directed to a specific target in insects, such as a receptor, the binding site might be changed by mutations so that the PSM can no longer bind to it (examples are Na^+, K^+ ATPase, or amino acyl tRNA synthetase). Other strategies involve a sequestration of a toxic PSM into a compartment where it does not affect the metabolism. Or the degradation of PSM with cytochrome p450 enzymes or their export via ABC transporters can be additional strategies. These adaptive mechanisms are not general but relevant for a single group of compounds. Thus, there are several beetles which can cope with the defense chemistry of seeds of a particular plant species but not with those of its leaves or roots [2, 8, 20, 21, 25, 26, 36, 37, 41].

On top of this, we have the specialization for nectar feeding in insects, several of which are also specific for a restricted selection of plant species. Thus, the evolution of a large number of angiosperm species probably offered many ecological niches for speciation of specialized insects.

As discussed before, the insects visiting a flower should not feed on the carpels or other parts of the flower, but only transfer the pollen, which they carry on their integument, to the stigma of the pistil. We can speculate that plants should protect their reproductive organ against herbivores. This is indeed the situation, and flowers usually harbor substantial amounts of PSM, which could function as repellents or deterrents. As mentioned before, many of the insect-pollinated angiosperms produce neurotoxic alkaloids, which also accumulate in all parts of the flower (only rarely in the nectar). Since neurotoxicity occurs immediately, such toxins should be well suited to ward off herbivores and to prevent a pollinating insect to feed on parts of the flower.

5 Conclusions

The abundance of alkaloid-producing plants among animal-pollinated angiosperms (Fig. 4) suggests that alkaloid evolution was enhanced during the last 150 million years when angiosperms started to radiate and to produce showy flowers that needed chemical protection. It is thus tempting to speculate that the evolution of alkaloids, but also of glucosinolates or cyanogenic glucosides in angiosperms, is the consequence of the co-evolution of angiosperms and pollinating insects or herbivores.

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