OCCURRENCE AND FUNCTION OF NATURAL PRODUCTS IN PLANTS

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Contents

Summary

Secondary metabolites (SM) occur in plants in a high structural diversity. A typical feature of secondary metabolites is their storage as complex mixtures in relatively high concentrations, sometimes in organs which do not produce them. Some SM are stored as inactive “prodrugs” that are enzymatically activated in case of danger (wounding, infection). Biochemical and physiological features of secondary metabolism are strongly correlated with its function: SM are not useless waste products but important means of plants for defense against herbivores, microbes (bacteria, fungi) and viruses. Some SM also functions as signal molecules to attract pollinating arthropods or seed-dispersing animals. Land plants have evolved SM with a wide repertoire of biochemical and pharmacological properties. Many SM interact with proteins, DNA/RNA and/or biomembranes. Some of the interactions with molecular targets are highly specific, others have pleiotropic properties. All plants produce secondary metabolites. Whereas some SM have a taxonomically restricted distribution, very often the same SM also occurs in other plant groups which are not phylogenetically related. How to explain the patchy distribution? Theoretically, the occurrence of a SM in unrelated taxa may be due to convergent evolution. Alternatively, the genes encoding the enzymes of secondary metabolism might be widely distributed in the plant kingdom but switched on or off in a certain phylogenetic context. The analysis of nucleotide and amino acid sequences, provide evidence that most of the genes, which encode key enzymes of SM biosynthesis have indeed a wide distribution in the plant kingdom. It is speculated that these genes were introduced into the plant genome during early evolution by horizontal gene

transfer, i.e. via bacteria that developed into mitochondria and chloroplasts. A patchy distribution can also be due to the presence of endophytic fungi, which are able to produce SM. The profile of plant secondary metabolites in a given plant is thus the result of a complex process that had evolved over the last 500 million years.

1. Classes and Numbers of Secondary Metabolites

A typical characteristic of plants and other sessile organisms, which cannot run away when attacked by enemies or which do not have an immune system to ward off pathogens, is their capacity to synthesize an enormous variety of low molecular weight compounds, the so-called secondary metabolites (SM) or natural product.

Type of secondary metabolite	**Approximate numbers***
Nitrogen-containing SM	
Alkaloids	21000
Non-protein amino acids (NPAAs)	700
Amines	100
Cyanogenic glycosides	60
Glucosinolates	100
Alkamides	150
Lectins, peptides, polypeptides	2000
SM without nitrogen	
Monoterpenes including iridoids (C10) **	2500
Sesquiterpenes C15)**	5000
Diterpenes (C20)**	2500
Triterpenes, steroids, saponins (C30, C27)**	5000
Tetraterpenes (C40)**	500
Flavonoids, tannins	5000
Phenylpropanoids, lignin, coumarins, lignans,	2000
Polyacetylenes, fatty acids, waxes	1500
Anthraquinones and other polyketides	750
Carbohydrates, organic acids	200

Table 1. Numbers of secondary metabolites reported from higher plants
*approximate number of known structures; **total number of terpenoids exceeds 22000 at present.

More than 100 000 SM have been identified by phytochemists, including many nitrogen-free (such as terpenes, saponins, polyketides, phenolics and polyacetylenes) and nitrogen-containing compounds (such as alkaloids, amines, cyanogenic glycosides, non-protein amino acids, glucosinolates, alkamides, peptides and lectins) (Table 1, Figure 1). All plants produce SM and usually store several major compounds, usually from different structural classes and biochemical pathways, which are commonly accompanied by dozens of minor components. It is typical to find complex mixtures, which differ from organ to organ, sometimes between individual plants and regularly between species. Within a single plant species 5000 to 20000 individual primary and

secondary compounds may be produced, although most of them as trace amounts which usually are overlooked in a phytochemical analysis.

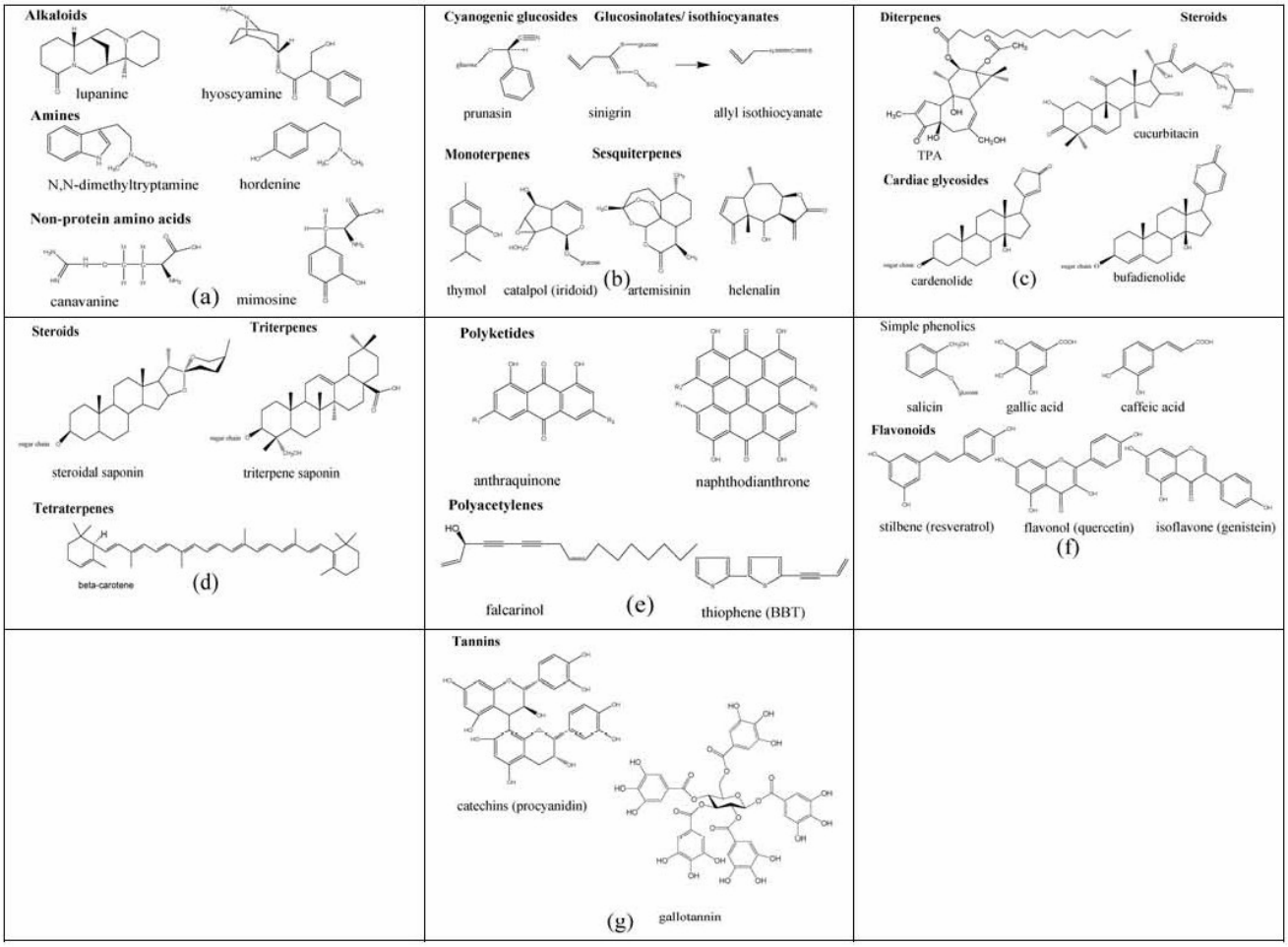

Figure 1. Structures of selected secondary metabolites.

2. Occurrence and Properties of Major Groups of SM

A**lkaloids** are widely distributed in the plant kingdom (especially angiosperms) and represent the largest group of SM that contain one or several nitrogen atoms either in a ring structure (true alkaloids) or in a side chain (pseudoalkaloids)**.** Chemically, alkaloids behave as a base; they are uncharged at alkaline pH (>11) and protonated under physiological conditions. The majority of alkaloids have been found to be derived from amino acids, such as tyrosine, phenylalanine, anthranilic acid, tryptophan/tryptamine, ornithine/arginine, lysine, histidine and nicotinic acid. However, alkaloids may be derived from other precursors such as purines in case of caffeine, terpenoids, which become “aminated” after the main skeleton has been synthesized, i.e. aconitine or the steroidal alkaloids, such as are found in the Solanaceae and Liliaceae. Alkaloids may also be formed from acetate-derived polyketides, where the amino nitrogen is introduced as in the hemlock alkaloid, coniine. Depending on the ring structures, alkaloids are subdivided into pyrrolidine, piperidine, pyrrolizidine, quinolizidine, isoquinoline, protoberberine, aporphine, morphinane, quinoline, acridone, indole,

monoterpene indole, diterpene or steroid alkaloids. The biosynthetic pathways of the main groups of alkaloids have already been elucidated at the enzyme and gene level.

Alkaloid are infamous as animal toxins and certainly serve mainly as defense chemicals against predators (herbivores, carnivores) and to a lesser degree against bacteria, fungi and viruses. Alkaloids and amines often affect neuroreceptors in animals as agonists or antagonists, or they modulate other steps in neuronal signal transduction, such as ion channels or enzymes, which take up or degrade neurotransmitters or second messengers. Since alkaloids often derive from the same amino acid precursor as the neurotransmitters acetylcholine, serotonin, noradrenaline, dopamine, gamma aminobutyric acid (GABA), glutamic acid or histamine, their structures can frequently be superimposed on those of neurotransmitters. They thus share functional pharmacological groups. Other alkaloids are mutagenic in that they intercalate DNA, alkylate DNA, induce apoptosis or inhibit carbohydrate processing enzymes. It is apparent that the toxicity of most alkaloids is correlated with their interactions with a particular molecular target.

Non-protein amino acids (NPAAs) are abundant in seeds, leaves and roots of legumes (Fabaceae) and in some monocots (Alliaceae, Iridaceae, Hyacinthaceae), but also occur in Cucurbitaceae, Euphorbiaceaee, Resedaceae, Sapindaceae, and Cycadaceae. They can be considered as structural analogues to one of the 20 protein amino acids. NPAAs frequently block the uptake and transport of amino acids or disturb their biosynthetic feedback regulations. Some NPAAs are even incorporated into proteins, since transfer ribonucleic acid (tRNA) transferases cannot usually discriminate between a protein amino acid and its analogue; resulting in defective or malfunctioning proteins. Other NPAAs interfere with neuronal signal transduction or enzymatic processes. NPAAs often accumulate in seeds where they serve as herbivore repellent nitrogen storage molecules, which are recycled during growth of the seedling after germination.

Cyanogenic glycosides have been recorded from more than 2000 plant species; they are especially abundant in Rosaceae, Fabaceae, Euphorbiaceae, Caprifoliaceae, Poaceae, Linaceae, Lamiaceae, Passifloraceae, Sapindaceae, Juncaginaceae and Ranunculaceae. Cyanogens are stored in the vacuole of seeds, leaves and roots as prefabricated allelochemicals ("prodrug" principle). If tissue decomposition occurs due to wounding by a herbivore or a pathogen, then a β-glucosidase comes into contact with the cyanogenic glucosides, which are split into a sugar and a nitrile moiety that is further hydrolyzed to hydrocyanic acid (HCN) and an aldehyde. HCN binds to cytochrome oxidase and therefore effectively blocks mitochondrial respiration; in consequence adenosine triphosphate (ATP) production is blocked. Therefore, HCN functions as a strong poison in most animals.

Glucosinolates also function as prefabricated vacuolar defense compounds. They occur in seeds, leaves and roots in a phylogenetically related complex, the Brassicales, which comprises the Brassicaceae, Capparaceae, Tropaeolaceae, Resedaceae, Moringaceae, and others. The glucosinolates are a precursor for the active mustard oils, which are released after cleavage by myrosinase. Mustard oils are highly lipophilic and can disturb the fluidity of biomembranes and bind to various enzymes, receptors or other macromolecules, such as DNA (thereby exhibiting a substantial antimicrobial effect).

Terpenes have a basic C5-unit (isopentenyl pyrophosphate or dimethylallyl pyrophosphate) as a building block and can be subdivided into monoterpenes (C10),

sesquiterpenes (C15), diterpenes (C20), triterpenes (C30), tetraterpenes (C40) and polyterpenes. Steroids are derived from triterpenes. Mono-, sesqui-, di- and triterpenes occur in most plant families; they are usually highly hydrophobic substances and are stored in resin ducts, oil cells or glandular trichomes. Most of them readily interact with biomembranes and membrane proteins. They can increase the fluidity of the membranes, which can lead to uncontrolled efflux of ions and metabolites, modulation of membrane proteins and receptors or even to cell leakage, resulting in cell death. This membrane activity is rather non-specific; therefore, terpenes show cytotoxic activities against a wide range of organisms, ranging from bacteria and fungi to insects and vertebrates. Many terpenes are even effective against membrane enclosed viruses. Even if the concentrations were not critical for a large vertebrate herbivore, terpene-rich food is usually avoided, since these terpenes would inhibit the growth of rumen microorganisms, which are important for the breakdown of cellulose. A number of terpenes have additional properties because their structures figure as analogues to natural substrates, hormones (e.g. steroidal hormones, sex hormones, ecdysone, juvenile hormone) or neurotransmitters. Sesquiterpene lactones, which are common in Asteraceae and a few other families (Apiaceae, Magnoliaceae, Menispermaceae, Lauraceae, and ferns), can bind to proteins with SH- groups and are therefore pharmacologically active. Several diterpenes are quite toxic; phorbol esters (present in Euphorbiaceae and Thymelaeaceae) activate protein kinase C and therefore cause severe inflammation. Grayanotoxin I (or andromedotoxin), which is common in Ericaceae is a potent inhibitor of sodium channels and thus a strong neurotoxin.

Saponins are the glycosides of triterpenes or steroids and include the group of cardiac glycosides and steroidal alkaloids. Steroid saponins are typical for monocots, especially for Dioscoreaceae, Melanthiaceae/Trilliaceae, Liliaceae, Agavaceae, Asparagaceae, Ruscaceae, Zingiberaceae, Alliaceae, Poaceae and Smilacaceae; they are less frequent in dicots (Fabaceae, Scrophulariaceae, Plantaginaceae, Solanaceae, Araliaceae). Triterpene saponins are abundant SM in Caryophyllaceae, Ranunculaceae, Phytolaccaceae, Chenopodiaceae, Styracaceae, Hippocastanaceae, Theaceae, Fabaceae, Apiaceae, Araliaceae, Asteraceae, Aquifoliaceae, Rosaceae, Polygalacdeae, Chenopodiaceae, Cucurbitaceae, Rhamnaceae, Primulaceae, Poaceae and Sapotaceae. They are absent in gymnosperms. Some saponins are stored as bidesmosidic compounds in the vacuole, which are cleaved to the active monodesmosidic compounds by β-glucosidase or an esterase upon wounding-induced decompartmentation. Monodesmosidic saponins are amphiphilic compounds, which can complex cholesterol in biomembranes with their lipophilic terpenoid moiety and bind to surface glycoproteins and glycolipids with their sugar side chain. This leads to a severe tension of the biomembrane and leakage. This activity can easily be demonstrated with erythrocytes, which lose their hemoglobin (haemolysis) when in contact with monodesmosidic saponins. This membrane activity is rather unspecific and effects a wide set of organisms from microbes to animals. Therefore, saponins have been used in traditional medicine as anti-infecting agents.

Some saponins have additional functional groups, such as cardiac glycosides (carrying a 5 or 6 membered cardenolide or bufadienolide ring), which enable them to inhibit one of the most important molecular targets of animal cells, the Na^+-, K^+-ATPase. Na^+-, K^+-ATPase builts up Na^+ and K^+ gradients which are essential for transport activities of cells and neuronal signaling. Therefore, cardiac glycosides are strong neurotoxins which

cause death through cardiac and respiratory arrest. Among steroidal glycosides, the cucurbitacins (occurring in members of the Cucurbitaceae) express substantial cytotoxic activities; they may interfere with the formation of the mitotic spindle during cell division.

Flavonoids and phenylpropanoids (including coumarins, furanocoumarins, catechins and tannins) are widespread in plants. They exhibit a wide range of biological activities. In several instances, they act as analogues of cellular signal compounds or substrates. Afflicted mechanisms range from prostaglandin and leukotriene formation, enzyme inhibition, estrogenic properties (coumarins, isoflavones, stilbenes) to DNA alkylation (e.g. by furanocoumarins). These molecules usually have several phenolic hydroxyl groups in common, which can dissociate in negatively charged phenolate ions under physiological conditions. Phenolic hydroxyl groups form hydrogen and ionic bonds with proteins and peptides. The higher the number of hydroxyl groups, the stronger the astringent and denaturing effect. Tannins inhibit enzymatic activities very effectively; however, most digestive enzymes of herbivores have apparently adapted to tannins during evolution and are less sensitive than other enzymes. Polyphenols are present in most drugs used in phytotherapy and apparently are responsible for a wide array of pharmacological properties, including antioxidant, anti-inflammatory, sedating, wound-healing, antimicrobial and antiviral activities.

Polyketides include anthraquinones, hydro- and naphthoquinones. Hydroquinones are typical for Ericaceae, naphthoquinones for Droseraceae, Iridaceae, Bignoniaceae, Juglandaceae, and Balsaminaceae. Anthraquinones are charactersitic for Polygonaceae, Rhamnaceae, Fabaceae, Rubiaceae, Hypericaceae, Scrophulariaceae, Asphodelaceae, and Liliaceae. Anthraquinones produce severe diarrhoea in vertebrates by interfering with intestinal Na^+, K^+-ATPase and adenylyl cyclase. The anthraquinones can intercalate DNA and appear to be mutagenic.

Polyacetylenes are characteristic for Apiaceae, Araliaceae and Asteraceae. Thiophenes, which are sulphur-containing polyacetylenes occur in the Asteraceae genera *Dahlia*, *Eclipta*, *Flaveria*, *Porophyllum*, *Rudbeckia*, *Tagetes*, and *Tessaria.* Because of the triple bonds these SM are highly reactive (often activated by light) and can interact with biomembranes and proteins. They are highly cytotoxic and sometimes neurotoxic; they also show antimicrobial activities.

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Biographical Sketch

Michael Wink was born in 1951 in Esch-Bad Münstereifel near Bonn (Germany). He studied biology, chemistry and statistics at the University of Bonn and obtained his "Diplom" in 1977. His PhD work was

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After 4 years as a lecturer (Hochschulassistent C1) he passed his "Habilitation" and got a Dr. rer. nat. habil. from Technical University of Braunschweig (Germany) in 1984/85. He was awarded a Heisenberg-fellowship from the German Science Foundation (DFG) in 1985 which he used to spend 6 months at the Max-Planck-Institute of Plant Breeding at Cologne (Germany). In 1986 he joined the "Gene Centre" of the University of Munich. In 1988 he accepted a chair for "Pharmaceutical Biology" at the University of Mainz and a year later a full professorship at Heidelberg University at Heidelberg (Germany). He is head of the Department Pharmaceutical Biology at the Institute of Pharmacy and Molecular Biotechnology. At Heidelberg University he served several terms of office as dean, vice dean or student dean and head of department. He was visiting professor at the universities of Cordoba (Argentina), Nanjing (China) and Hat-Yai (Thailand) and was offered an Honorary professorship of the University of Harbin (China). He runs a large research group, working on natural products, their analytics, function and pharmacology, biotechnology and evolution (phylogeny, molecular taxonomy). He has published more than 20 books or monographs and more than 500 papers in peer-reviewed international journals.

Prof. Dr. Michael Wink. He is a member of several professional societies of phytochemistry, medicinal plants, evolution, botany, pharmacy and ornithology.