Chapter

Biosynthesis of Natural Products

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Abstract

Natural products are in the form of primary and secondary metabolites and are isolated chemical compounds or substances from living organisms. Terpenes, Phenolic compounds, and Nitrogen-containing compounds are secondary metabolites. The biosyntheses of secondary metabolites are derived from primary metabolism pathways, which consist of a tricarboxylic acid cycle (TCA), methylerythritol phosphate pathway (MEP), mevalonic and shikimic acid pathway. This chapter provides an overview of the diversity of secondary metabolites in plants, their multiple biological functions, and multi-faceted cultural history.

Keywords: natural products, biosynthesis, metabolites, phytochemicals, terpenes, phenolic compounds, nitrogen-containing compounds

1. Introduction

Natural products are lead compounds, which are frequently produced by plants and microbes as their secondary metabolites, and securing large quantities of such compounds for industrial and clinical applications has been a persisting problem [1]. Natural products (chemical compounds or substances) are isolated from living organisms [2]. Biogenesis belief that complex living things come only from other living things and also the production of new living organisms or organelles using reproduction. Chemistry of natural product is produced by the pathway of primary or secondary metabolism [3]. Metabolism is used to describe all chemical reactions which include maintaining the living state of cells of an organism [4]. Metabolism can be in form of catabolism or anabolism. Metabolites are a product of metabolism and restricted to small molecules [5].

Plants produce natural products with highly diverse structures; these products are called "secondary metabolites" in contrast to the "primary metabolites", which are essential for plant reproduction, and growth. The leaf, stem, root, or bark of the plant has plant secondary metabolites that have been produced, for example Alkaloids, Tannins, Flavonoids, and Phenolic compounds [6]. Most food, spices and herbs are indigenous plants has these secondary metabolites [7]. Plant secondary metabolites are exclusively produced by more than 30,000 different plants. They serve as defense compounds against pathogens and herbivores, as flower pigments that attract pollinators. Natural products have a strong impact on human culture and are used throughout human history as pigments, condiments, and pharmaceuticals [8].

This chapter therefore provides an overview of the biosynthesis of natural products, their multiple biological functions and multi-faceted cultural history.

2. Classification of plants secondary metabolite

Plants secondary metabolites can be classfied into three groups namely

- Terpenes
- Phenolic compounds
- Nitrogen-containing compounds [8]

2.1 Terpenes

Terpenoids constitutes the largest class of secondary products; they comprise of more than 40,000 different structures and are the largest natural products in plants [9, 10]. Terpenes consists of five-carbon isoprene units, and classified into hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), triterpenes (C_{30}), tetraterpenes (C_{40}), and polyterpenes [11, 12]. Terpenoids originate from two different biosynthetic routes: plastid-located deoxyxylulose phosphate (DXP) pathway (also called methylerythritol phosphate or MEP pathway) and the cytosolic mevalonic acid (MVA) pathway (**Figure 1**) [13–15].

2.1.1 Hemiterpenes

This is a volatile compound synthesized from DMAPP, isoprene is the most abundant true hemiterpene from plants (**Figure 2**). The species that synthesize isoprene are found among ferns, mosses, angiosperms, and gymnosperms. The emission and production of isoprene are distributed very widely in the plant kingdom. Isoprene is emitted into the atmosphere and protects leaves to survive short periods of high temperature. Moreover, it increases the plant's tolerance towards ozone and reactive oxygen species [16]. Hemiterpenes may also act as signaling molecules. The highly volatile hemiterpene methacrolein are emitted in the leaves of sagebrush (*Artemisia tridentata*) (**Figure 2**) in addition to other volatile compounds like hexenal, monoterpenes, and methyl jasmonate when the plant is damaged, this

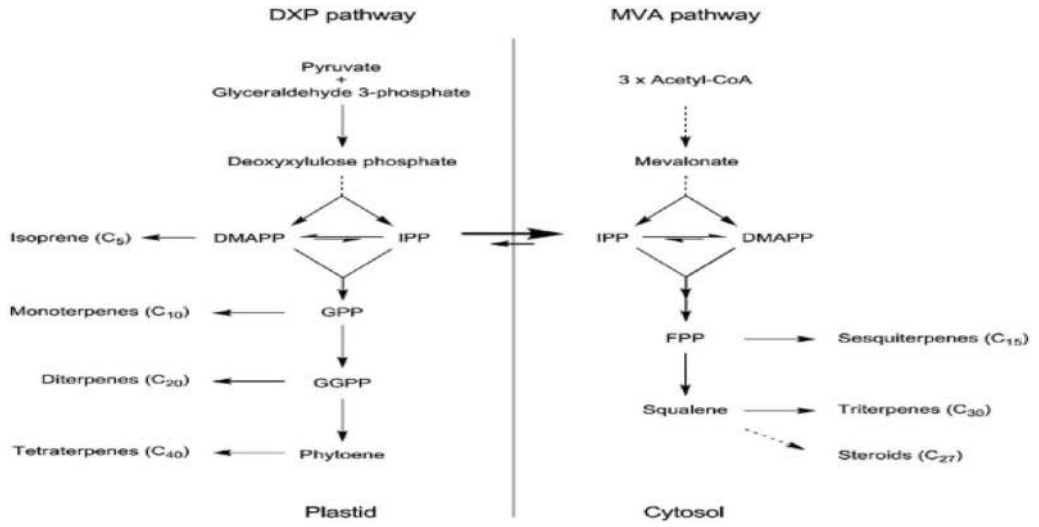

Figure 1.
Schematic overview of terpene biosynthesis in plants.

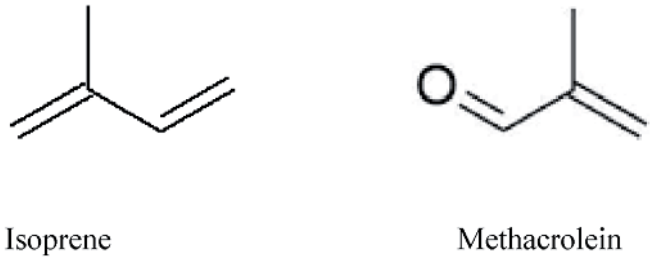

Figure 2.
Hemiterpenes.

is perceived by plants and enables them to react faster to a possible attack. A plant that is prepared in this manner is less likely to be damaged by herbivores [17]. The C-5 units derived from DMAPP are found in natural products of mixed biosynthetic origin, e.g., hop bitter acids, prenylated flavonoids, and hyperforin.

2.1.2 Monoterpenes

Monoterpenes originate from one molecule DMAPP and one molecule IPP that are joined in most cases head-to-tail, yielding all- trans geranyl diphosphate (GPP) (**Figure 3**). Several plant families, e.g., the Lamiaceae and Asteraceae, have glandular trichomes with secretory cells that produce terpenes and secrete them into a shared subcuticular storage cavity [18]. Conifers accumulate a complex mixture of mono-, sesqui-, and diterpenes, oleoresin, in resin blisters or ducts, which are covered by a layer of epithelial cells that secrete and synthesize the terpenes into the lumen [19]. As in the case of the conifers, many other plants accumulate monoterpenes in mixtures containing the larger sesqui- and diterpenes, rather than monoterpenes alone. The physiological function of monoterpenes is defense, the attraction of pollinators, and plant–plant communication [20]. The plant-insect interactions role of terpenes has been well-studied in conifers and the bark beetle. The oleoresin is secreted from the ducts or produced newly upon tissue damage by the beetle [21]. Ingested monoterpenes are converted by the beetles to pheromones that either attract more beetles or serve as anti-aggregation signals. Besides, conifer monoterpenes take part in tritrophic interactions and attract insect predators that feed on bark beetles [19]. Most aromatherapy, insecticides, perfumes and pharmaceutical products are made from monoterpenes [18]. The essential oil of corn mint (*Mentha arvensis* var. piperascens) produce more than 7000 tons of menthol every year either by total synthesis or from the steam-distilled. The cooling sensation stimulated by menthol is caused by the excitation of cation channels that serve as thermal receptors [22]. Two monoterpenes with promising anticancer effects are perrillyl alcohol and (+)-(R)- limonene [23], these two compounds

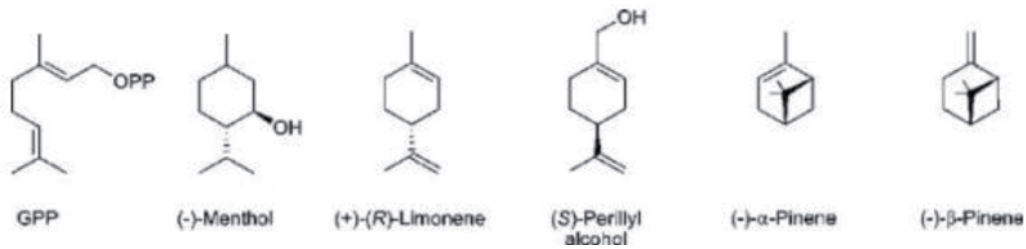

Figure 3.
Mono- and bicyclic monoterpenes derived from geranyl diphosphate (GPP).

suppress translation of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, an enzyme of the MVA pathway and induce apoptosis [24]. The 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase enzyme is a promising target for anti-tumor compounds because tumor cells have elevated HMG-CoA reductase levels and many proteins involved in cell growth are phenylated. The decreased terpene biosynthesis in humans leads to suppression of HMG-CoA reductase [25]. The secoiridoids yields from the cleavage of the cyclopentane ring of the iridoid skeleton, which are monoterpene indole alkaloids and the biosynthetic building units of the Ipecac alkaloids [25]. Many iridoids have an intense bitter-taste and therefore act as feeding deterrents (**Figure 4**) [26].

2.1.3 Sesquiterpenes

In general, sesquiterpenes are less volatile than monoterpenes; they contain three isoprene units and are formed by condensation of DMAPP with two molecules IPP, the central C_{15} intermediate farnesyl diphosphate (FPP) can be folded into mono-, bi- or tricyclic systems [9]. Initially, it was assumed that all sesquiterpenes are produced via the cytosolic MVA pathway. Recent studies, however, revealed that certain sesquiterpenes originate from isoprene units provided by the DXP pathway [12, 13] or by both biosynthetic routes [27]. This can be explained by the transport of isoprenoid precursors from the plastids to the cytosol [28]. Abscisic acid is a sesquiterpene phytohormone that is induced by drought and promotes stomatal closure and seed dormancy. Other sesquiterpenes take part in tritrophic plant-herbivore-parasite interactions [13]. The sesquiterpenes (E)-b-farnesene and the (E)-a-bergamotene attract the parasitic wasp *Cotesia marginiventris*, in maize infested with lepidopteran larvae [29]. Maize roots release (E)-b-caryophyllene (**Figure 5**) upon an attack of larvae of the beetle *Diabrotica virgifera* to attract the parasitic nematode *Heterorhabditis megidis* [30]. Many sesquiterpenes (sesquiterpene lactones) contain a pentacyclic lactone group, these compounds occur abundantly in the family Asteraceae, because of their bitter taste sesquiterpene lactones presumably serve as feeding deterrents of herbivores [31]. Pharmacologically active sesquiterpene lactones often show anti-inflammatory effects due to inhibition of the transcription factor NF- kB that mediates immunological responses and inflammation [32]. One of the most popular medicinal plants, chamomile (*Matricaria recutita*) is a sesquiterpenes with such activities. Antimigraine action of some sesquiterpene lactones, e.g., parthenolide from feverfew (*Tanacetum parthenium*), is mediated by inhibition of platelet aggregation and serotonin secretion [9]. The reason for the cytotoxicity

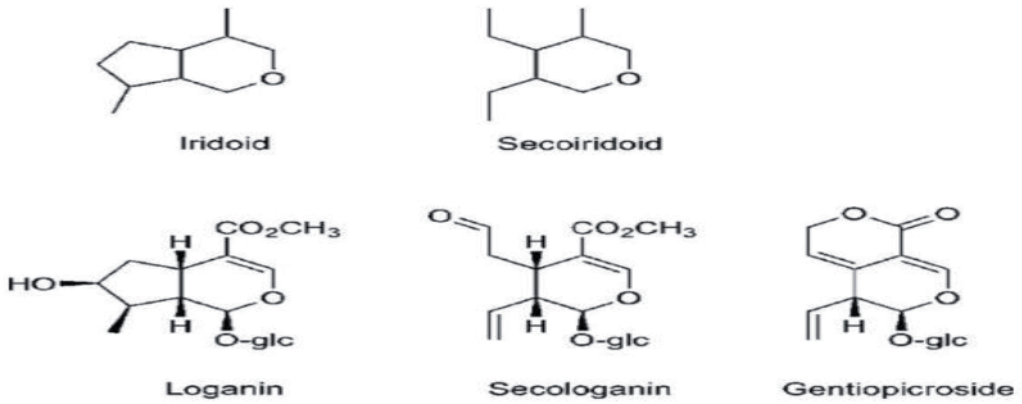

Figure 4.
Iridoids.

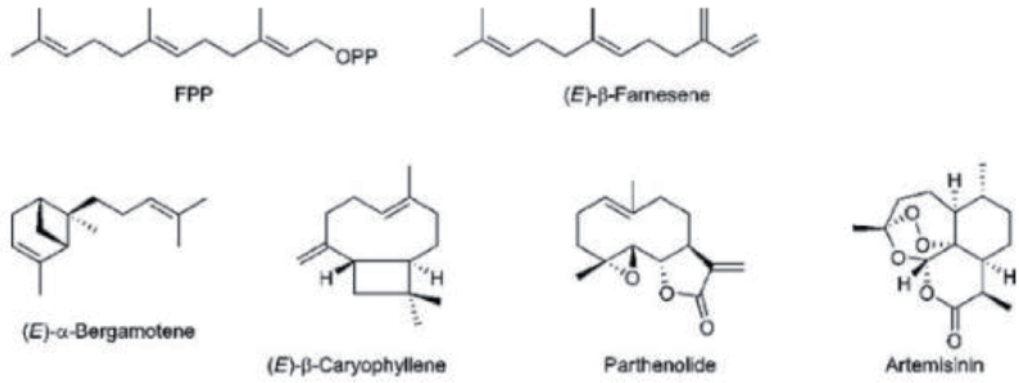

Figure 5.
Linear and cyclic sesquiterpenes.

and allergenicity of sesquiterpene lactones with a, b-unsaturated lactone is the alkylation of proteins. Artemisinin is a novel promising agent against malaria. Structurally, it is a tetracyclic sesquiterpene with a six-membered lactone ring and an unusual 1, 2, 4-trioxane ring (**Figure 5**). The president of North Vietnam, to the Chinese government (Ho Chi Minh) discovered artemisinin for a cure against malaria to support his troops in the malaria-infested jungles during the American/Vietnamese war [33]. The ether extract from *A. annua*, and artemisinin (qinghaosu) revealed the antimalarial activity and the mode of action of artemisinin are still being investigated. Most likely, it interferes with sarco-endoplasmic reticulum calcium ATPase (SERCA) of *Plasmodium falciparum*, but other mechanisms, for example, alkylation of biological macromolecules or the production of reactive oxygen species [34]. The structural feature required for antimalarial activity is the peroxide bridge. Artemether and artesunate (two semisynthetic analogs), in efficiency comparison to artemisinin were developed and are now used as first-line therapy in the treatment of malaria, in combination with other antimalarial drugs like the lumefantrine and quinine analogs mefloquine. This combination tends to prevent resistance to Plasmodium. The artemisinin and its analogs success has triggered by extraction of the sesquiterpene from the plant because *A. annua* contains only 0.01–1.5% of artemisinin [35]. Therefore, an powerful and affordable drug for the people in malaria-endemic areas are necessary, either by breeding of *A. annua* plants with elevated artemisinin levels or biotechnological production of the artemisinin precursor artemisinic acid by cloning the biosynthetic genes from *A. annua* [35] and engineering the pathway into the bacterium *Escherichia coli* or yeast [36, 37].

2.1.4 Diterpenes

Diterpenes originate from the Plasmid DXP pathway and are synthesized from DMAPP and three molecules IPP yielding the C_{20} metabolite geranyl geranyl diphosphate (GGPP). GGPP is a smaller terpene; it can undergo rearrangements and cyclization to many different structures and also a precursor of the lipophilic phytyl side chain of chlorophyll and plastoquinone. Gibberellins are tetracyclic diterpenes that act as phytohormones and promote shoot elongation, flowering and seed germination [38]. Diterpenes like abietic- and levopimaric acid (**Figure 6**) are constituents of conifer oleoresin and function as a defense against herbivores and pathogens. After mono- and sesquiterpenes (turpentine) are removed from oleoresin by distillation, the solid diterpene fraction (rosin) is called colophonium. The mono and sesquiterpene containing distillate are used as oil of turpentine for the

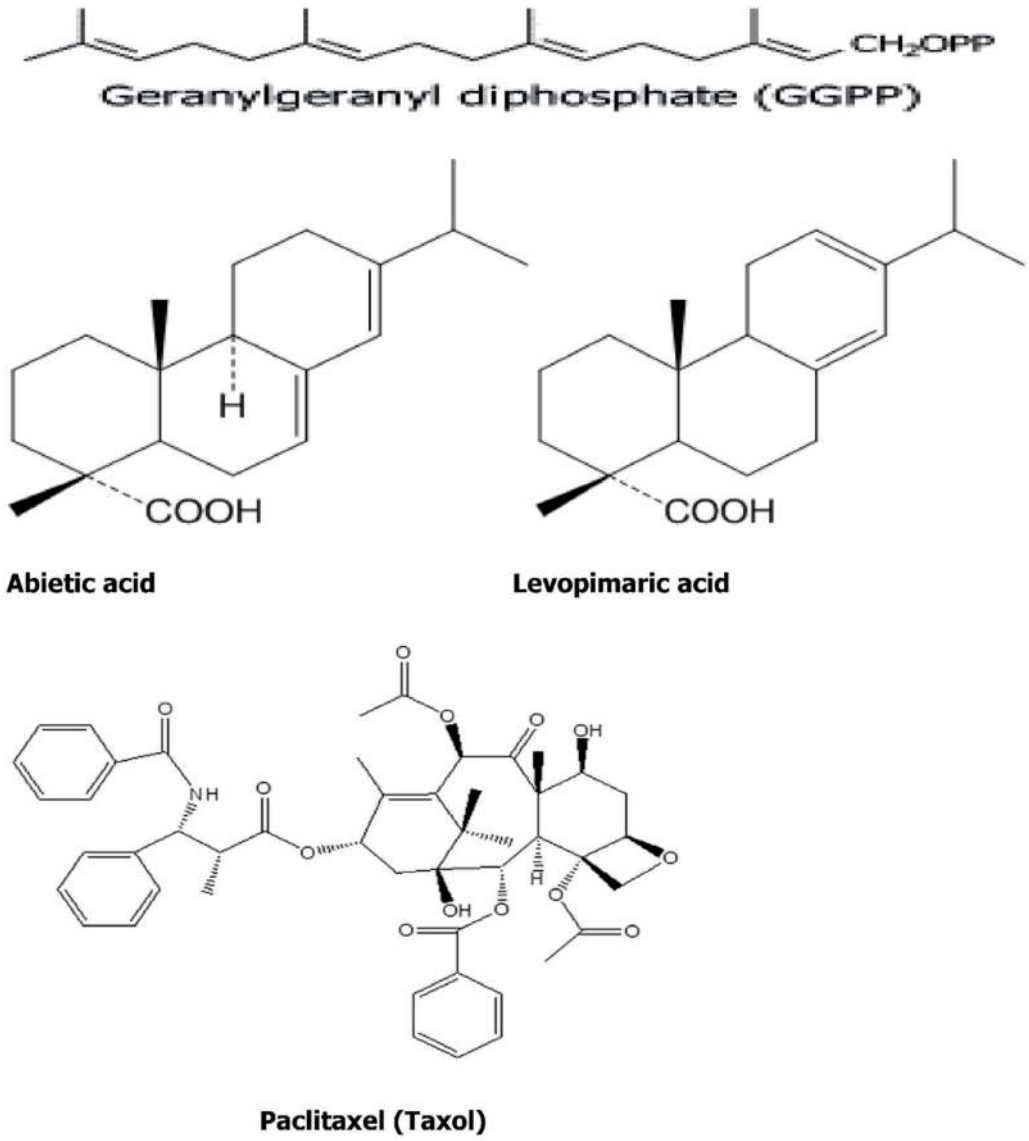

Figure 6.
Diterpenes.

thinning of paints and varnishes [39]. Paclitaxel binds to microtubules, stabilizes them against depolymerisation and thus blocks cell proliferation [40]. Paclitaxel is used in the therapy of cancers (breast, ovarian, lung, head and neck and Kaposi's sarcoma). In the bark of *T. brevifolia* (0.01–0.02%), paclitaxel occurs only in relatively low amounts and the trees grow slowly, other sources had to be found to supply enough of the diterpene for industrial production. Paclitaxel is obtained either by semisynthesis from baccatin III and 10-deacetylbaccatin III or from tissue cultures of various Taxus species, which can be extracted from the leaves and twigs of the common yew (*T. baccata*), a tree that grows much faster than *T. brevifolia* (**Figure 6**).

2.1.5 Triterpenes and steroids

Triterpenes are synthesized from two molecules of FPP that are joined by tail-to-tail condensation to squalene via the MVA pathway. Various structures, mostly tetra- or pentacyclic yields from cyclization of its metabolite 2, 3-oxidosqualene

followed by rearrangements and methyl shifts. The precursor of plant steroids is 2, 3-Oxidosqualene (**Figure 7**). In this case, it is cyclized to the triterpene cycloartenol, which is then converted to the C-27 compound cholesterol with the loss of three methyl groups. In both triterpenes and steroids the oxygen of 2, 3-oxidosqualene is usually retained as hydroxy group at C-3. Phytosterols are lipophilic and are readily incorporated into the micelles involved in fat digestion. Esters of phytosterols are therefore used as cholesterol-lowering food additives [9]. A group of plant hormones (Brassinosteroids) is derived from campesterol. They regulate various biological processes, e.g., stem elongation, leaf expansion, seed germination, and xylem differentiation [38, 41].

2.1.6 Saponins

Monocots preferably accumulate steroidal saponins, which are abundant in the Agavaceae, Dioscoraeceae, and Yuccaceae. Triterpenoid saponins contain the lupane skeleton, tetracyclic dammarane backbone as aglycone and the pentacyclic a-amyrin (ursane), b-amyrin (oleanane). This aglycone is linked with one to three carbohydrate chains containing up to six sugar molecules or uronic acids [9, 42]. In the triterpene backbone, the first sugar chain is attached to the hydroxy group at C-3. When two or more carbohydrate chains are present, they are connected with carboxy or hydroxy groups at C-30 or C-28. Spirostanols and furostanols are two groups of steroid saponins. A tetrahydrofuran ring in furostanols is formed from the side chain of cholesterol, and the hydroxy group at C-26 is glycosylated. Upon cleavage of this sugar moiety, a second oxygen-containing heterocycle is formed, thus yielding a spirostanol (**Figure 8**). As in the case of the triterpene saponins, steroidal saponins carry a sugar chain at the C-3 hydroxy group [41, 43–47].

2.1.7 Tetraterpenes

Tetraterpenes are synthesized from two molecules GGPP by tail-to-tail addition and comprise only one group of compounds, the carotenoids. The tetraterpene chain is cyclized to a six-membered ring at either one or both ends. Carotenoids with hydroxy or epoxy functions are classified as xanthophylls [9]. The important physiological functions of carotenoids in plants, is that it act as accessory pigments of chlorophyll, since they are part of the light-harvesting complex. Besides, they quench triplet oxygen and singlet oxygen in case of excess light energy and thus protect the plant from photo-oxidative damage. As pigments of flowers and fruits,

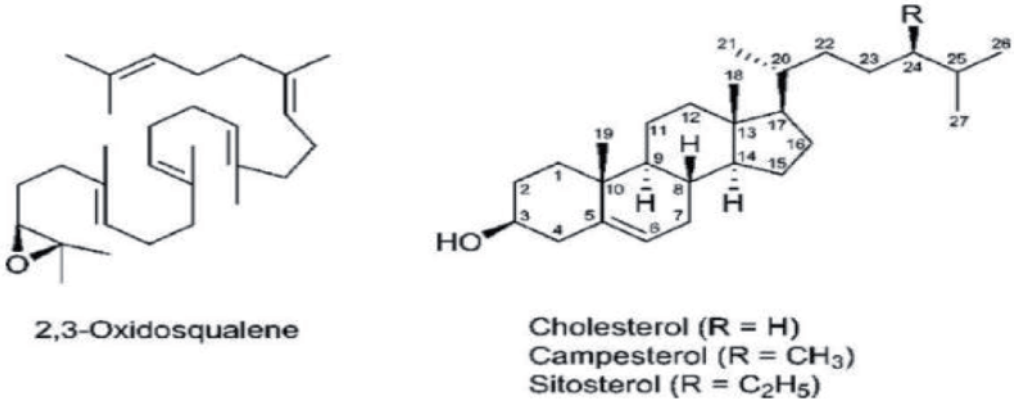

Figure 7.
Sterols derived from 2, 3-oxidosqualene.

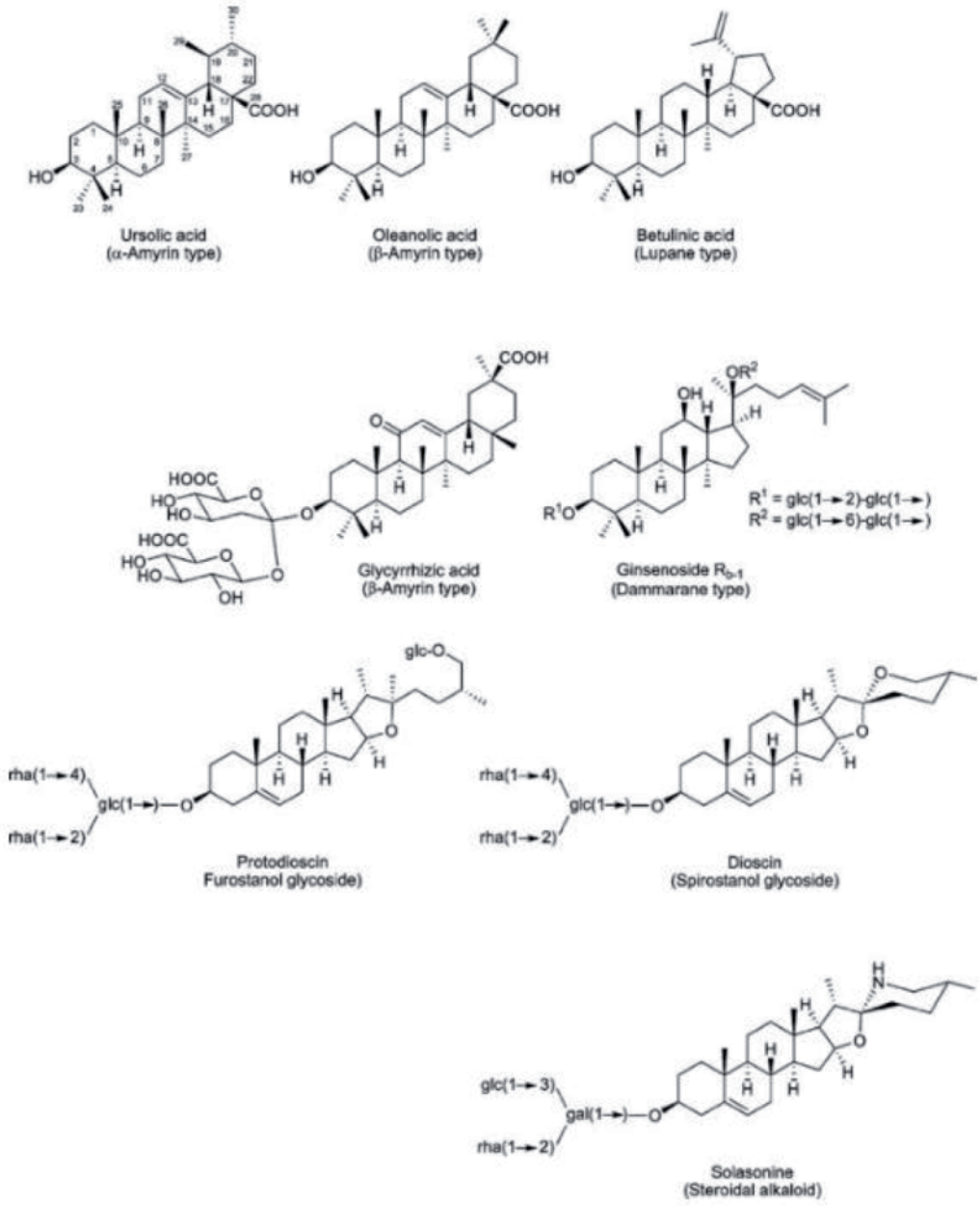

Figure 8.
Triterpene and steroid saponins.

carotenoids attract pollinators and seed dispersers [48]. Carotenoids (a-carotene, b-carotene) are essential for human health (**Figure 9**), b-cryptoxanthine is precursors of vitamin A. They serve as the pigment of the light receptors of the human eyes, and converted in the liver to vitamin A. To overcome vitamin A deficiency in areas with malnutrition, transgenic rice termed, golden rice "was developed that expresses high levels of carotenoid biosynthetic enzymes in the endosperm and accumulates elevated levels of carotenoids [49–51].

2.2 Phenolic compounds

Phenolic compounds (phenolic acids and polyphenols) are derivatives of the shikimic, pentose phosphate, and phenylpropanoid pathways in plants [52].

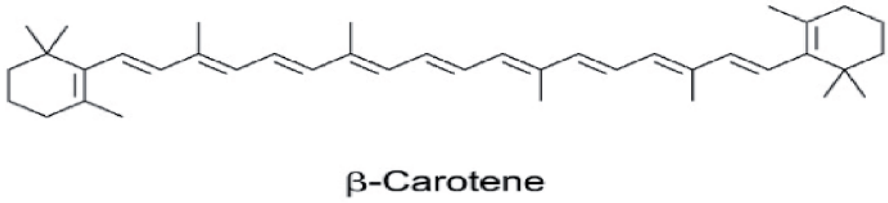

Figure 9.
β-Carotene.

Polyphenols are aromatic ring which contains a phenyl group and a hydroxyl functional group [53]. Plant phenolic compounds are lignin, flavonoids, carotenoids, tannins, and phytoalexins; they are responsible for antioxidant, antiaging, antiproliferation and anti-inflammatory activities. Vegetables, fruits and beverages are major sources of phenolics [54, 55]. Tannins significantly reduce the growth of many herbivores when added to their diets because they are generally toxic. Tannins can be seen in fruits like apples, blackberries, tea and red wine [56]. Tannins are mainly constituent of woody plants especially heartwood. Some derivatives of tannin include Gallic acid [56].

2.2.1 Phenol derivatives, especially flavonoids

The biosynthetic pathways are derived from the shikimate pathway (**Figure 10**), which is shared by indoles, and by several alkaloids and betalains. The phenylalanine

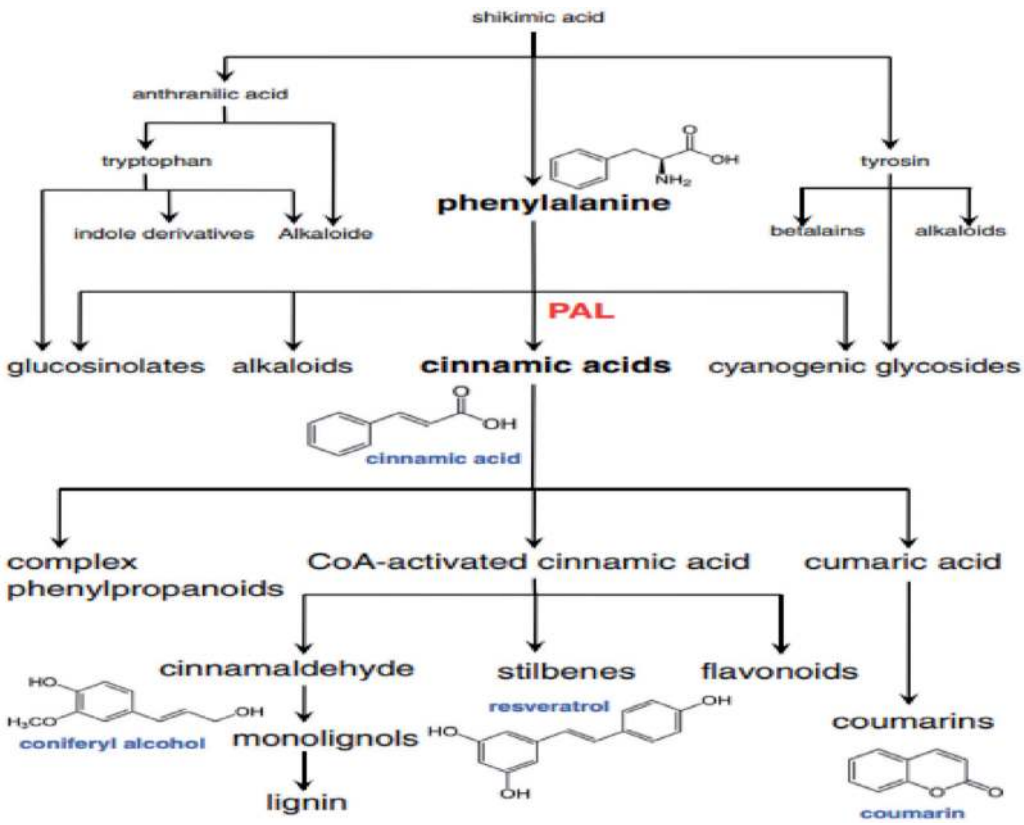

Figure 10.
Schematic overview for the biosynthetic pathways of selected phenols from phenylalanine as a precursor (bold). A key enzyme, phenylalanine ammonia-lyase (PAL), is shown (red). Some example structures are depicted (blue) [57].

is the precursor for the cinnamic acid derivatives and flavonoids, and it is converted by an enzyme, phenylalanine ammonia-lyase (PAL) to cinnamic acid. Rosmarinic acid has high antioxidative potential and also good aromatic qualities. The cinnamic acid derivatives serve as precursors for polymers (lignin), which is synthesized via cinnamaldehydes and monolignols. Much information is also available from maize and a legume, the latter also contains isoflavonoids (**Figure 11**). Other mutants in the pathway of, for example, the next enzyme encoding chalcone isomerase (which is responsible for the synthesis of naringenin), also show this phenotype, and consequently, the mutations were numbered consecutively, starting with "1." Mutations in the transcription factors that control the synthesis of flavonoids have similar phenotypes [57].

2.3 Nitrogen-containing compounds

Alkaloids are heterocyclic nitrogen compounds biosynthesized from amino acids. Alkaloids represent one of the biggest groups of natural products, with currently more than 12,000 known structures. In addition to alkaloids, benzoxazinoids, glucosinolates, and cyanogenic glucosides will be represented. Like alkaloids, these

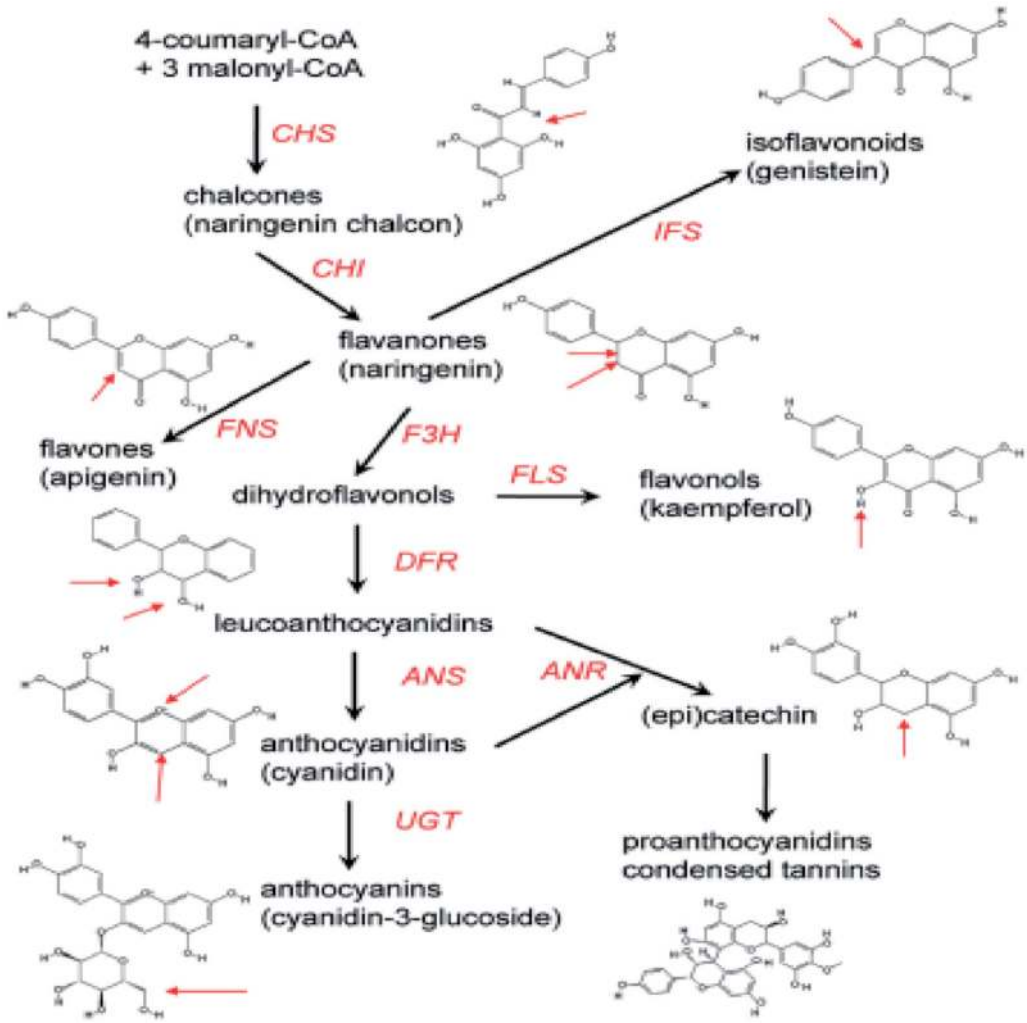

Figure 11.
The main pathways for flavonoid synthesis derived from different plant species. CHS: chalcone synthase; CHI: chalcone isomerase; IFS: isoflavonoid synthase; FNS: flavone synthase; F3H: flavanone-3- hydroxylase; FLS: flavonol synthase; DFR: dihdroflavonol reductase; ANS: anthocyanidin synthase; UGT: glycosyltransferase; ANR: anthocyanidin reductase [57].

metabolites contain nitrogen and are derived from amino acids. Morphine is an alkaloid isolated in 1805 from opium poppy *Papaver somniferum* [58, 59]. The role of alkaloids in the plant has been a subject of speculation for at least 100 years. Most alkaloids are now believed to function as a defense against especially mammals, because of the general toxicity and deterrence capacity [60]. One group of alkaloids, the pyrolizidine alkaloid illustrates how herbivores can become adapted to tolerate plant defensive substances and even use them in their defense [60].

2.3.1 Alkaloids

Alkaloid was introduced by a German Chemist, Carl F.W Meissnerin in 1815. Alkaloids are Alkali-like and derived from the word Alkali. They are a group of naturally occurring organic compounds which are basic, contain one or more nitrogen atoms normally of Heterocyclic nature. They also possess specific physiological actions on the human and animal bodies and are abundant in higher plants (Angiosperm). Major types of alkaloids and their examples are represented in **Table 1**. Families rich in alkaloids are- Apocynaceae, Rubiaceae, Solanaceae, Papaveraceae, Berberidaceae, etc. Alkaloids are present in many parts of the plant- Aerial part (Ephedra – Ephedrine), Entire plant (Vinca- Vincristine, Vinblastine), Leaves (Tea- Caffeine), Root (Rauwolfia- Reserpine), Bark (Cinchona- Quinine), Seed (Nuxvomica), Fruit (Black pepper- Piperine), Latex (Opium- Morphine, Codeine). Pharmacological uses include; Anagelsic, Antimalarial, Antispasmodic, Hypertension, Mental disorder, Anticancer etc. Alkaloids occur mainly in plants as Salts of organic acid (oxalic acid, citric acid, acetic acid, maleic acid, tartaric acid, fumaric, benzoic, etc). Functions in plants include; protective against insects and herbivores (bitterness and toxicity), a product of detoxification (a waste product) in a certain case, a reservoir for protein synthesis, and a source of nitrogen in case of deficiency. Many precursors are involved in various pathways, such as aromatic amino acids (tryptophan, tyrosine and phenylalanine), and also aspartate, glutamine, lysine, glycine and valine (**Figure 12**). Besides, the nonproteinogenic amino acid ornithine is an important precursor for various alkaloids.

Type	Plant source	Example	Uses
Pyrrolidine	Leaves of *Peruvian coca* shrub	Hygrine	Stimulants, Depressant
Tropine	*Atropa belladonna*	Atropine, Cocaine	Antidote of poison
Piperidine	Bark of bomegranate, Oil of hemlock. *Conium maculatum*	Coniine	Poison (paralyzes of motor neuron)
Pyramidine-pyridine	Tobacco leaf *Nicotina tabacum*	Nicotine	Respiratory stimulation
Quinoline	Cinchona tree	Quinine	Treatment of malaria
Isoquinoline	*Papaver somniferum* Seed of nuxvomica Strychnos	Codeine, morphine	Treatment of cough and Analgesic
Indole	*Claviceps purpurea*	Strychnine, Reserpine, Psilocybin	Treatment of hypertension, uterine atonia, postpartum bleeding, hallucination
Pyridine-piperidine	*Anabasis aphylla*	Anabasine	Antimicrobial, antioxidant

Table 1.
Major types of alkaloids [53].

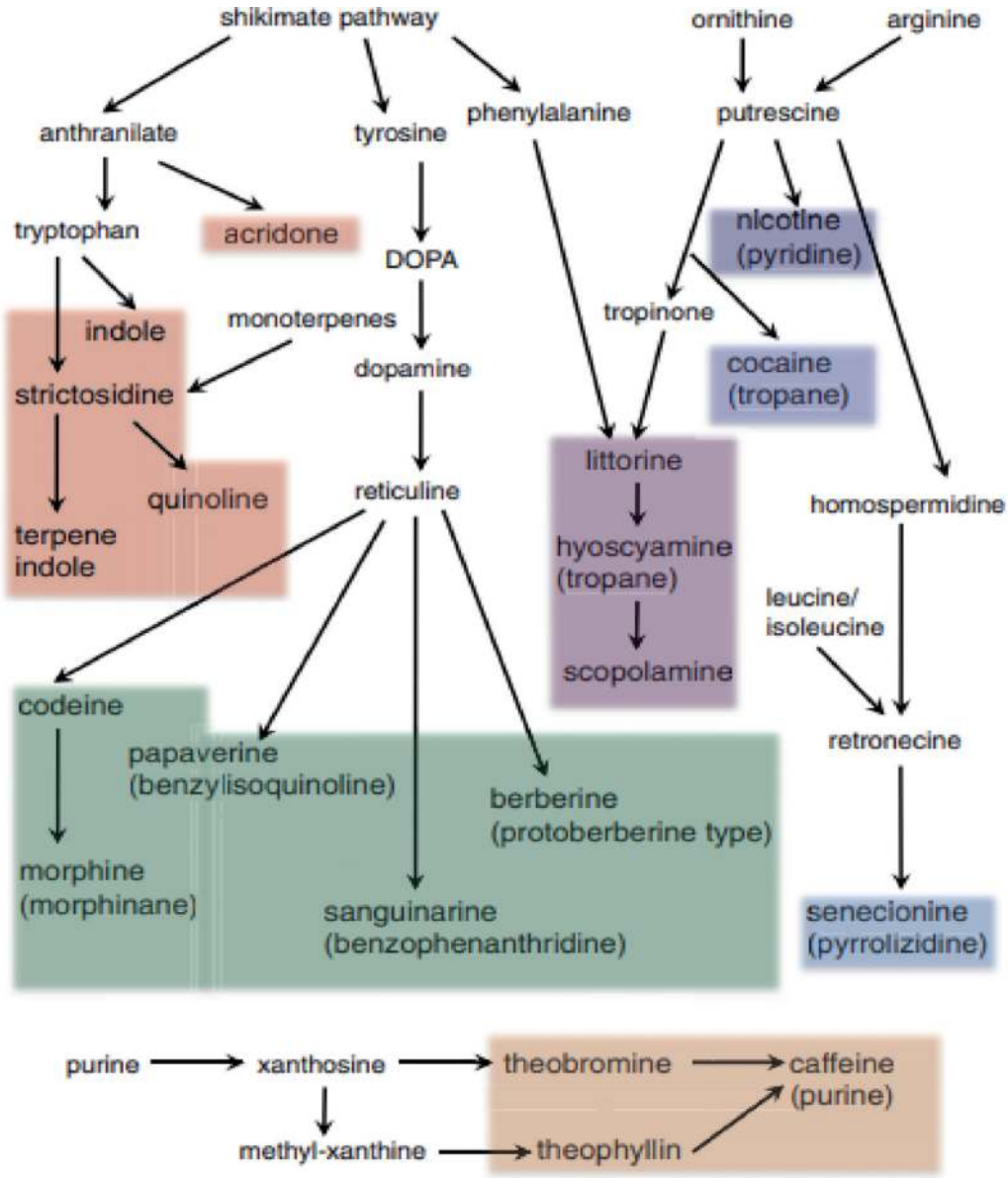

Figure 12.
Overview of the biosynthesis of selected alkaloids. Phenylalanine together with ornithine is needed for the synthesis of the second group of tropane alkaloids (violet). Caffeine and related substances are derived from purine (brown). The class of compounds is given in brackets [57].

For several alkaloids, two different precursors are needed for the biosynthetic pathways. In the case of terpene indole alkaloids (**Figure 12**), it is not only tryptophan that is involved as a precursor for the indole moiety, but also monoterpenes for the synthesis of side chains. Another example is the biosynthesis of the tropane alkaloids hyoscyamine and scopolamine, where ornithine and phenylalanine are required for the different parts of the molecule (**Figure 12**) [57].

2.3.2 Benzoxazinones

Benzoxazinones is a class of natural products known as cyclic hydroxamic acid, found in wheat, rye and maize in the family of Gramineae [61]. They act as plant resistance to insects and microbes. At present, it is still being investigated

whether the pathway developed only once or several times independently after the divergence of monocots and dicots [62, 63]. Besides, they serve as feeding deterrents and reduce the vitality of pests. In particular, these metabolites confer resistance to one of the major corn pests, the European corn borer (*Ostrinia nubialis*) [64]. The mode of action of benzoxazinones can be explained by the modification of amino and thiol groups of biomolecules. The aldehyde function of the tautomeric open-ring form can react as an electrophile with NH_2 groups and form Schiff bases [65]. The structural prerequisite for this oxidation is an electron-donating substitution at C-7 of the benzoxazinone skeleton (**Figure 13**) [66]. Benzoxazinoids that have been bio-activated by N -acetylation may act as alkylating agents towards nucleic acids and proteins. Due to their toxicity, benzoxazinones can also function as allelochemicals and are therefore discussed as natural herbicides [67].

2.3.3 Glucosinolates

Glucosinolates are b -thioglucosides of (Z) - N - hydroximinosulfate esters (**Figure 14**). They share the first steps of cyanogenic glucoside biosynthesis. About 120 different structures of glucosinolates are known [68]. The glucosinolates are hydrolyzed by myrosinase (if the plant tissue is damaged), a thioglucosidase is spatially separated in the undamaged tissue [69] (**Figure 14**). The main product of the "mustard bomb" consisting of glucosinolates and myrosinase is isothiocyanates. These compounds are also responsible for many of the biological effects of glucosinolates, e.g., antibacterial, antifungal, nematicidal, and feeding deterrent activities [68]. The formation of hydrolysis products distinct from thiocyanates depends on the structure of the glucosinolates, pH, and the presence or absence of Fe^{2+} ions or specifier proteins [70]. Hydrolysis of b -hydroxyalknyl glucosinolates yields oxazolidine-2-thiones that can cause goiter by inhibiting the incorporation of iodine into thyroid hormones. To make the protein-rich seed cake that remains after the extraction of the oil suitable as animal foodstuff, Grape plants with low levels of glucosinolates have been developed by breeding efforts [68]. Sulforaphane enhances the excretion of cancerogenic compounds by inducing glutathione-S-transferase, UDP-glucuronosyl transferase, and NADPH quinone oxidoreductase (phase II detoxification enzymes) [70, 71]. The glucosinolates act as feeding deterrents, and many insect herbivores feed on plants containing these natural products. The detoxification of glucosinolates is known from two insect species which has two very different mechanisms [72]. The cabbage white butterfly (*Pieris rapae*) contains a specified protein that transforms glucosinolates in the presence of myrosinase to nontoxic nitriles that are excreted with the feces [73]. This requires either an endogenous myrosinase that is spatially separated from the glucosinolates in the insects or myrosinases from the gut microflora of their enemies [69].

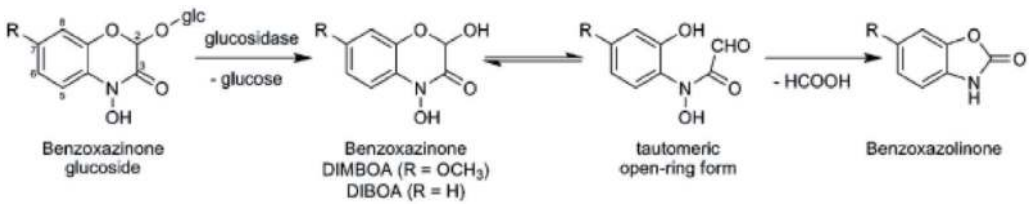

Figure 13.
Enzymatic and chemical degradation of benzoxazines with hydroxamic acid function [61].

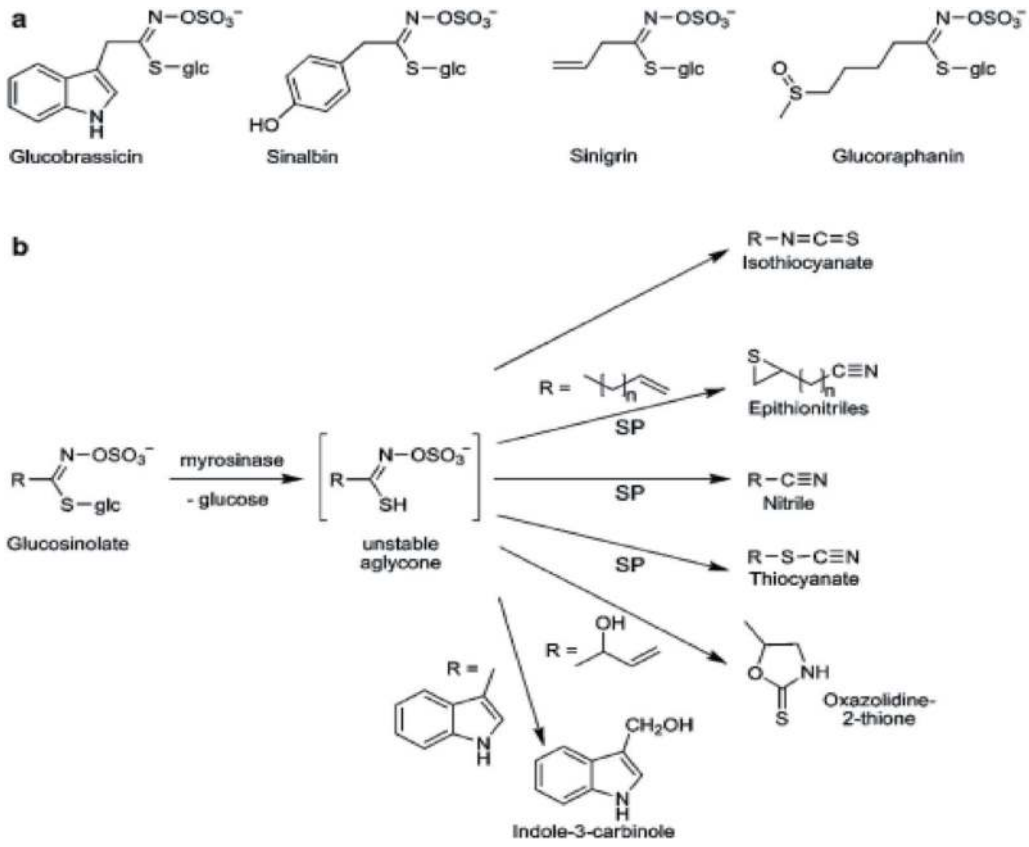

Figure 14.
Exemplary structures of glucosinolates (a) and hydrolysis of glucosinolates by myrosinase and rearrangement to various products (b) Isothiocyanates are the predominant degradation products.

2.3.4 Cyanogenic glycosides

Cyanogenic glucosides are b-glucosides of a–hydroxy nitriles (syn. cyanohydrins), which are derived from the five proteinogenic amino acids phenylalanine, tyrosine, valine, isoleucine, leucine, and the non-proteinogenic amino acid cyclopentenyl-glycine. About 2500 different plant species including ferns, gymnosperms, and angiosperms produce cyanogenic glycosides [74, 75]. Despite their widespread occurrence, these natural products are found predominantly in the families Araceae, Asteraceae, Euphorbiaceae, Fabaceae, Passifloraceae, Poaceae, and Rosaceae [9, 76]. Some of the most abundant molecules are amygdalin (Rosaceae), linamarin and lotaustralin (Fabaceae), and the epimers dhurrin and taxiphyllin in the genus Sorghum [75]. The b-glucosidic bond can also be hydrolyzed by intestinal bacteria in the gut of herbivores. The hydrogen cyanide toxicity can be explained by its affinity to metal ions. Cyanide ions complex iron (III) in the active site of cytochrome oxidase thus inhibits the respiratory chain [77, 78]. Cyanogenic glucosides act as feeding deterrents, by transferring all genes required for the formation of the cyanogenic glucoside dhurrin from *Sorghum bicolor* into Arabidopsis, proved that cyanogenic glucosides play a role in plant defense [79, 80]. Several herbivores, especially insects, can feed on plants containing these natural products, despite the toxicity of the cyanogenic glucosides, and the toxic compounds may act as phagostimulants. Cyanogenic glucosides act as defense compounds for some species of beetles, centipedes, and millipedes, but particularly many moths and butterflies (**Figure 15**). The compounds are either taken up by feeding on cyanogenic plants or synthesized by endogenous enzymes [77, 78]. It has been postulated that cyanogenic

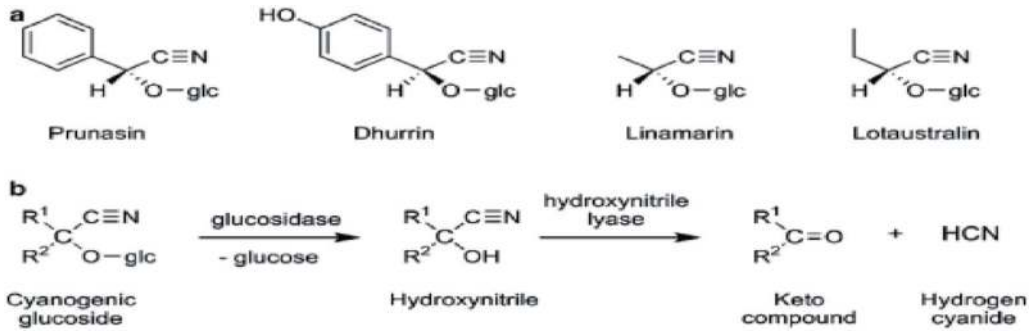

Figure 15.
Representative structures of cyanogenic glucosides (a) and degradation of cyanogenic glucosides with concomitant release of toxic hydrogen cyanide (b).

glucosides also serve as storage compounds for reduced nitrogen and sugar [81, 82]. These treatments often results in loss of protein, minerals, and vitamins. Various approaches to produce transgenic cassava with reduced content of cyanogenic glucosides in roots are currently underway [76, 80, 83, 84].

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