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Review

The effect of ultraviolet radiation on the accumulation of medicinal compounds in plants

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ABSTRACT

A review is given of how the production by plants of compounds useful as medicines or raw materials for manufacture of medicines is influenced by ultraviolet radiation, particularly by UV-B radiation (280–315 nm wavelength). The compounds considered in this review are flavonoids and other phenolics, alkaloids (especially indole terpenoid and purine alkaloids), essential oils and other terpenoids, cannabinoids, glucosinolates and isothiocyanates, and compounds having human hormone activity. A short account is also given of ultraviolet signalling in plants. The review concludes with a discussion of the possible evolutionary mechanisms that have led to the evolution of UV-B regulation of secondary metabolite accumulation.

Contents

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1. Introduction

Despite progress in synthetic chemistry, plants still constitute an important source of pharmaceuticals and other compounds of economic importance. Fowler [1] estimates that 25% of prescription medicines are derived directly or indirectly from plants. The secondary metabolism producing these compounds is not only species-specific, but depends on various environmental factors. Ultraviolet radiation is one important factor that in many cases stimulates the production of secondary metabolites. The part of the ultraviolet daylight spectrum that is particularly variable, and therefore worth paying special attention to, is the UV-B band, 280–315 nm.

There is no general health benefit in exposing food plants to extra UV-B radiation [2], except for a small amount of vitamin D obtainable in this way. This review will deal specifically with medicinal plants, i.e. those producing substances used as medicines or used as raw materials for medicines.

As stated by Laurain-Mattar [3] "While it is generally possible to introduce most plants into tissue culture, the production of adequate levels of particular secondary metabolites, like alkaloids, may be problematic." In some cases the reason for this may be that ultraviolet radiation is absent from the cultures. Secondary metabolites have often been obtained in callus and cell cultures when UV-B (radiation of wavelength 280–315 nm) or UV-C (wavelength <280 nm; usually mostly 254 nm) radiation has been applied [4–8]. In most of the experiments related below the radiation has, unfortunately, not been properly quantified and characterized.

2. Ultraviolet signalling in plants

Compared to what is known about how plants sense blue, red and far-red light, the elucidation of perception of ultraviolet-B radiation has been slow, and much has still to be done. Contributing to difficulties in defining the radiation-absorbing chromophores and the signalling pathways are the following circumstances: (a) compared to the long-wavelength regions of the daylight spectrum, the number of cell constituents absorbing in the ultraviolet region is very large, and (b) suitable irradiation systems for action spectroscopy in the ultraviolet region are expensive.

As far as we know today, plants sense UV-B radiation in at least four different ways:

2.1. Photogeneration of reactive oxygen species (ROS) and sensing of these by the plant

There are many photochemical reactions that can result in ROS production, and therefore action spectra may vary with plant material and circumstances. Different photochemical processes can generate different kinds of ROS, which can function in different ways. ROS can also be generated via excitation of one of the UV-B receptors under 2.3 or 2.4 below, activating nitrogen monoxide (NO) signalling and NADPH oxidase [9]. The role of ROS in UV-B signalling has been explored particularly by A.-H.-Mackerness and coworkers [10–12].

2.2. Photodamage to DNA (nucleotide dimer formation)

That such damage constitutes the start of a signalling pathway was first indicated by experiments by Beggs et al. see also Beggs and Wellmann [13,14], who showed that the action spectrum for synthesis of the isoflavonoid coumestrol in *Phaseolus vulgaris* leaves peaks in the UV-C region. The UV effect was counteracted by visible light which allowed photorepair of DNA. A recent article showing that a similar process accounts for UV induction of resistance against an oomycete parasitizing *Arabidopsis* is that by Kunz et al. [15]. The induction of transcription of the β-1,3-glucanase in bean leaves [16] is probably an analogous phenomenon. Also in this case DNA repair inhibits the induction of transcription.

2.3. Absorption of radiation in a specific UV-B receptor with maximum absorption in the 280–290 nm range

This receptor [17] requires a fluence rate of at least 0.1 μmol m^{-2} s^{-1} for signal transduction [18]. This transduction chain activates genes requiring HY5 and HYH transcription factors via UVR8. UV-B radiation both promotes the transport of UVR8 from cytosol to nucleus and the interaction of UVR8 with chromatin [19]. The UV-B induced remodeling of chromatin necessary for UVR8 activation may involve histone acetylation via (or in combination with) UV-B activated proteins [20,21].

2.4. Absorption of radiation in another specific UV-B receptor with maximum absorption in the 300–310 nm range

This receptor [17] requires an approximately tenfold higher fluence rate than the previous receptor [18]. This signal transduction chain includes WRKY30, FAD oxidoreductase, and UDP-glucuronosyl/UDP-glucosyl transferase family protein.

In most of the cases described below there is not enough information available to distinguish between cases 2.1 to 2.4. The common use of the term "stress" in conjunction with increased accumulation of secondary metabolites is not always warranted. In most of the cases radiation effects on growth are not described. When effects are described [22,23] there were no or very small effects on growth, except for Brechner [24], who found a ca. 70% reduction in final plant weight due to the radiation dose she used. As for flavonoids, one can even find cases, such as *Colospermum mopane* f. alba [25] and *Pisum sativum* L cv. Meteor [26] in

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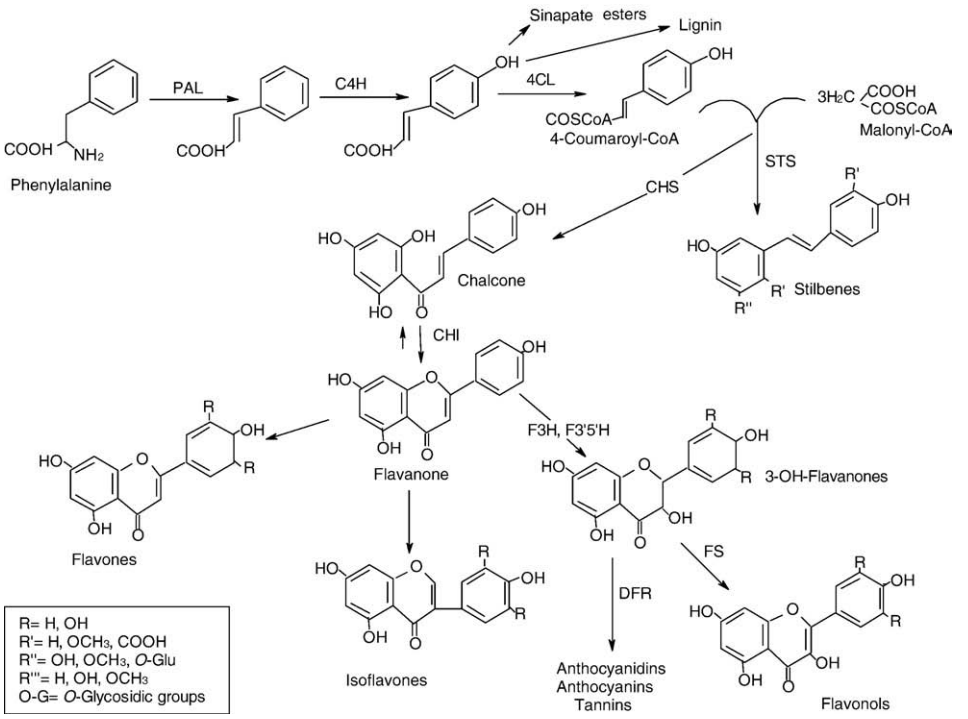

Fig. 1. Biosynthesis of flavonoids and related compounds. From Shirley [30], modified.

which not only these compounds, but also growth is increased by UV-B radiation.

3. Flavonoids

"Flavonoid" is a term that is a bit ambiguous; literally it means "flavone-like compound", so we can start with the structure of flavone (Fig. 1). Flavonoids in a strict sense are compounds with this ring skeleton and various side groups. However, many people use flavonoids in a wider sense and include other compounds, such as isoflavonoids and anthocyanidins. These compounds often occur in plants as glycosides, and also these glycosides may be included in the term flavonoids. We shall use here the term flavonoid in a wide sense.

Flavonoids have long been considered beneficial for health. Originally their good effects were thought to be due to their "antioxidative" effect and also their radical scavenging ability. Conversely others have been considered to be useful in cancer therapy because they stimulate the production of reactive oxygen species and thereby cause cell death [27], or cause cell death in other ways [28]. All flavonoids are not equally good

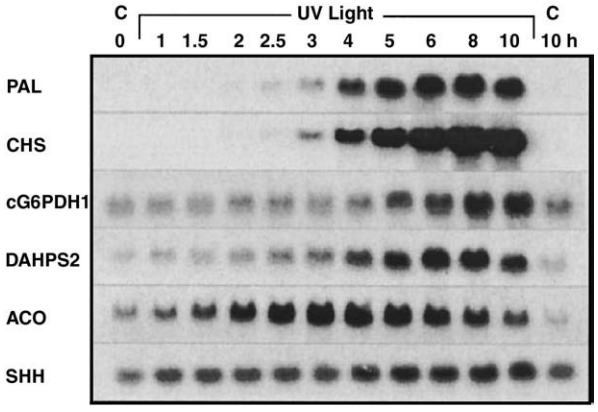

Fig. 2. Parsley (*Petroselinum crispum*) cell cultures were exposed to ultraviolet radiation for the indicated number of hours; control (C) unexposed for 1 or 10 h. RNA samples were taken at various times and hybridized with DNA of the indicated genes: PAL, phenylalanine ammonia lyase; CHS, chalcone synthase; cG6PDH1, an isozyme of glyceraldehyde 3-phosphate dehydrogenase; DAHPS2, a form of 3-deoxy-D-*arabino*heptulosonate 7-phosphate synthase; ACO, acyl-CoA oxidase; SHH, *S*-adenosyl-homocysteine hydrolase. The "UV light" is a mixture of UV-A and visible light. From [31]. Copyright 2000 National Academy of Sciences, U.S.A.

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for the health, and some can even be poisonous. For details about the health effects of flavonoids the reader is referred to Ross and Kasum [29].

Flavonoids are the classical UV-B-regulated compounds in plants, and their biosynthesis and its regulation have been very thoroughly explored [30,31]. Phenylalanine ammonia lyase (PAL) and chalcone synthase (CHS) are enzymes in the flavonoid biosynthetic pathway which have long been known to be UV-B inducible, but at least in parsley (*Petroselinum crispum*) genes for several other enzymes of importance for early steps in flavonoid biosynthesis, such as glucose 6-phosphate dehydrogenase, 3-deoxy-D-arabino heptulosonate 7-phosphate synthase, and S-adenosyl-homocysteine hydrolase, are also under UV control (Fig. 2).

One of the most important sources of flavonoids in the diet of many people is tea. Some published investigations show differences in the quality of the tea, including flavour and flavonoid content with the season of harvesting. These differences could be due to changes in ambient ultraviolet-B radiation with the season, but also to other factors, so more clearcut evidence needs to be obtained before it can be stated that there is an effect of UV-B in this case. Another important diet component for many people is buckwheat (*Fagopyron esculentum*). This crop contains the flavonoid rutin, which is considered beneficial for the health. Kreft et al. [32] found that the ambient UV-B radiation in Slovenia during summer was optimal for rutin accumulation. Both increase and in particular decrease of the radiation lowered the content. This paper also cites some other investigations providing indirect evidence for the importance of the UV-B environment.

Many isoflavones (see Fig. 1) are active as estrogens in the human body. This will be dealt with in Section 11.3 Phytoestrogens below.

4. Stilbenes

As can be seen in Fig. 1, stilbenes and their derivatives are on a biosynthetic pathway related to that of flavonoids. Ku et al. [5] found that synthesis of substances of this kind, namely piceatannol and resveratrol, is also promoted by UV radiation (they used UV-C) in callus cultures of groundnut (peanut, Fig. 3). Piceatannol is used as an anticancer drug. Resveratrol is produced by many plants, and is considered to be a health-promoting substance in red wine.

Schmidlin et al. [33] found that a whole range of stilbene derivatives, including resveratrol, are induced in leaves of grapevine (*Vitis vinifera*, Cabernet Sauvignon variety) by UV-C (6 min, 254 nm, 90 mW cm^{-2}), and to a much lesser extent by infection with *Plasmopara viticola*, a downy mildew oomycete.

Resveratrol, 3,4′,5-trihydroxystilbene is biosynthesized in many plants, especially as a response to stress. It is particularly well known as a component in many red wines, but also in many white wines and other plant products. It is regarded as having multiple health-promoting effects [34] with potential in cancer and inflammatory disease therapy [35,36], heart disease [37,38] and neurodegenerative disease [39]. Resveratrol occurs in two isomeric forms, cis-resveratrol (or *Z*-resveratrol) and trans-resveratrol (or *E*-resveratrol). Most laboratory experiments on cell cultures etc. are done with *E*-resveratrol, which is commercially available. Natural products, on the other hand, generally contain both forms,

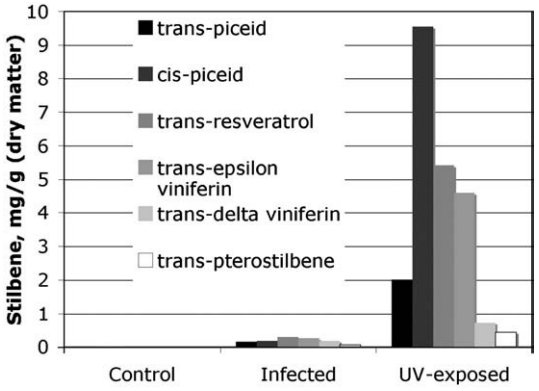

Fig. 3. Stilbene derivatives in grapevine leaves after infection with mildew fungus or exposure to UV-C radiation, compared to control. Induction by radiation is much more efficient than induction through infection. From Schmidlin et al. [33].

and for such products it is in most cases not clear which of these forms has the beneficial effects. In the rare cases when the two isomers have been compared, some effect differences have been noted [40].

Trans-resveratrol is the form first synthesized by the plant, and the cis-form can appear only as a result of a photochemical trans–cis isomerization, which requires UV-A radiation with wavelength below 360 nm. The conversion back to the trans-form takes place in darkness, although very slowly. It can be achieved more rapidly using UV radiation of a wavelength below 350 nm. The quantum yield for the trans to cis isomerization varies from about 0.07 in a very polar solvent as methanol to about 0.18 in a nonpolar solvent as hexane. The reverse cis to trans isomerization has a rather solvent independent quantum yield of about 0.35 [41]. A side reaction accompanying the latter is ring-closure to form 4α, 4β-dihydrophenanthrene.

Thermal conversions are very slow at ordinary temperatures, and based on rate measurements above 80 °C it can be estimated that the rate constant for cis- to trans-isomerisation at 25 °C is on the order of 10^{-10} s^{-1}, and the rate constant for the reverse reaction less than 1% of this. The equilibrium mixture consists of more than 99% of the trans-form, so all cis-form present in plants or plant products as wine must have been formed photochemically [42]. The photo-equilibrium cis/trans ratio under most daylight conditions is about 2:3 (the ratio depends on ozone layer thickness and solar zenith angle; for an ozone layer of 300 DU we calculated the following ratios for various solar zenith angles: 0.69 for 20°, 0.68 for 40°, and 0.64 for 60°; the daylight spectra for these conditions were calculated using the "Quick TUV calculator" at http://cprm.acd.ucar.edu/Models/TUV/). The ratio found in grapes and wines, on the other hand, is mostly around 0.1, i.e. far from both dark equilibrium (<0.01) and daylight photoequilibrium.

5. Other phenolics

Rosemary: Luis et al. [43] found that 31 kJ m^{-2} day^{-1} plant-weighted UV-B radiation (a very high daily exposure) approximately doubled the total phenolics content of rosemary plants compared to plants grown without UV-B.

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The contents of naringin, rosemarinic acid, cirsimaritin and carnosic acid doubled, while carnosol showed a fivefold increase. Caffeic acid was practically absent from unirradiated plants, but was present at a concentration of almost 3 mg (g fresh weight)$^{-1}$ in the irradiated plants. Vanillic acid and hispudilin did not increase; the latter one actually showed a decrease in the irradiated plants. One beneficial effect attributed to the rosemary phenolics is radical scavenging. Rosmarinic acid, caffeic acid and carnosic acid are effective scavengers, while vanillic acid and naringin are inefficient. Thus the scavenging efficiency of rosemary is greatly increased by high UV-B exposure. The biosynthetic pathway is shown in Fig. 4.

Likewise Zagoskina et al. [44,6] found phenolics in callus cultures of the tea plant to be increased by UV-B radiation.

Safflower (safflower thistle), *Carthamus tinctorius*, (not to be confused with saffron, which in some languages has a similar name) is a traditional medicinal plant in China (known as Flos Carthamni), Japan (known as Kouka or Mogami-benibana) and Korea [45]. Medical [45–48] and antimycotic [49], but also mutagenic [50] effects of preparations from it are described in modern literature [51]. An excellent Internet site with beautiful pictures and general information about safflower is <http://www.uni-graz.at/~katzer/engl/Cart_tin.html>.

Safflower oil is known for its high content of unsaturated fatty acids. Safflower thistle has also been used for dying, as it contains the red polyphenol pigment carthamin.

It has been found that the content of carthamin in *Carthamus* flowers can be increased by ultraviolet radiation. At the (unknown) dosages used, UV-C (254 nm) had a stronger effect than did UV-B [52–54]. Most likely the effect of the ultraviolet radiation is to generate hydrogen peroxide or other reactive oxygen species, which by oxidative decarboxylation convert the yellow precarthamin to red carthamin, as the conversion can also be brought about by hydrogen peroxide or enzymes generating hydrogen peroxide [55].

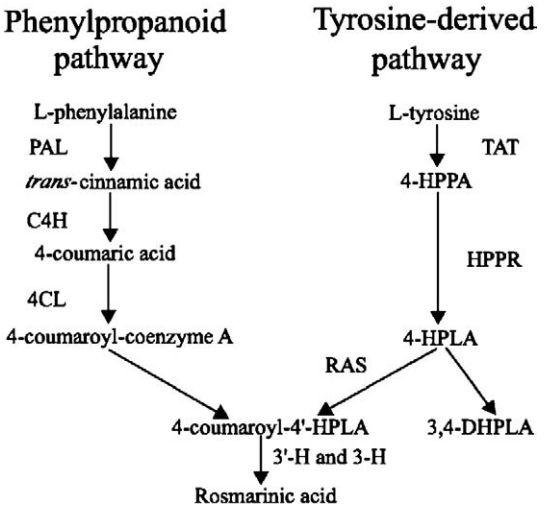

Fig. 4. Biosynthesis of rosmarinic acid in *Coleus blumei*. From Huang et al. [Huang B, Duan Y, Yi B, Sun L, Lu B, Yu X, Sun H, Zhang H, Chen W. C. Russian Journal of Plant Physiology 2008: 55:390.] after Petersen et al. [Petersen M. Hausler E, Karwatzki B, Meinhard J. 1993. Planta 1993:189:10.]. Enzymes in this pathway which are induced by UV-B are phenyl-ammonia-lyase (PAL) and *trans*-cinnamate 4-hydroxylase (C4H). 4CL, hydoxycinnamate; TAT, tyrosine transferase; HPPR, hydroxyphenylpyruvate reductase; 4-HPPA, 4-hydroxyphenylpyruvic acid; RAS, rosmarinic acid synthase; 3′-H and 3-H, hydroxycinnamoyl-hydroxyphenyllactate 3′- and 3-hydroxylases; and 3,4-DHPLA, 3,4-dihydroxyphenyllactic acid.

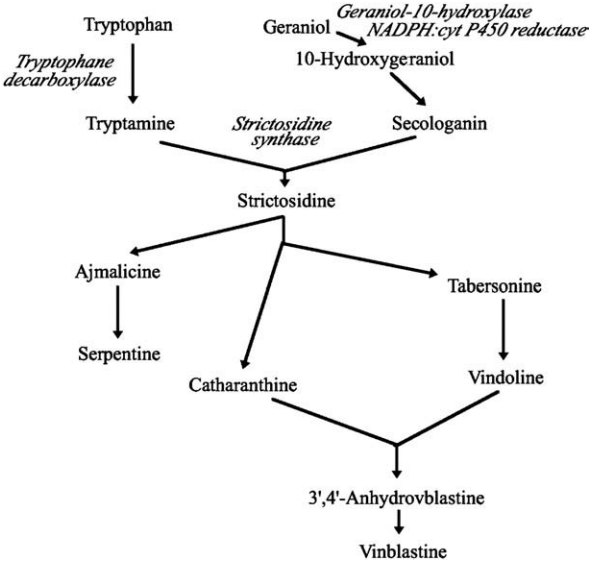

Fig. 5. Biosynthesis of indole terpenoid alkaloids in *Catharanthus roseus*. From [59], redrawn and slightly modified.

It is not with certainty known which, if any, of the medicinal effects of saffron are due to catharantin, but there are some indications that certain effects can be ascribed to catharantin [51], while other components are responsible for other effects [56].

6. Alkaloids

Alkaloids are low-molecular weight nitrogen-containing organic compounds. They usually have heterocyclic structures and occur in approximately 20% of all plant species. The number of identified structures has been variously estimated as 12,000 [57] or more than16,000 [58]. There are a number of different alkaloid groups that are not closely related chemically. We shall deal here with two of them, indole alkaloids and purine alkaloids.

6.1. Indole alkaloids

Indole alkaloids are in part derived from tryptophan, and in many important cases (examples are cataranthine, brachyserine and camptothecin detailed below) contain a terpenoid part derived from mevalonate via geraniol. Probably both these branches of the synthesis of the alkaloid molecules (Fig. 5) are stimulated by UV-B. Tryptophan decarboxylase, the enzyme catalyzing the first step on the indole branch, is induced by UV-B radiation [59], and so is strictosine synthase [60], which is also required for indole alkaloids. Regarding UV-B effects on the terpenoid branch, see Section 3. Flavonoids above.

Catharanthus roseus (Apocynaceae) and related plants contain more than 70 alkaloids, of which several, such as

vincristine, vinblastine and catharanthine (Fig. 4), are of medical interest (mainly for treating such cancers as leukemia and lymphoma). Several of them can now be produced synthetically. Ouwerkerk et al. [59] showed that the synthesis of several of the alkaloids in *C. roseus* is stimulated by ultraviolet radiation. The largest increase, 161% (i.e. 261% of the control, more than a doubling) was obtained for strictosidine. Ramani and Chelliah [60] have explored the signalling pathways leading to increased synthesis of catharanthine. UV-B-induced increase in alkaloid content may be the reason that whitefly shuns UV-B-irradiated plants [61].

Brachycerine is an indole monoterpenoid alkaloid produced by *Psychotria brachyceras* (Rubiaceae), but in a very low amount (≈0.25% by dry weight) unless it has received UV-B radiation [62]. Sixteen days of UV-B exposure brings the concentration in the leaves to 1.8% by dry weight. The substance quenches singlet oxygen, and thereby has antioxidant and antimutagenic effects [63].

Camptothecin is an indole terpenoid alkaloid produced by *Camptotheca acuminata* (Nyssaceae). It is used as an anticancer drug (review by Ulukan and Swan [64] because of its ability to inhibit DNA topoisomerase I [65]. After three weeks treatment Li and Liu [66,67] obtained up to 70% increase per seedling in the production of this substance by intermittent exposure to UV-C radiation during the night.

6.2. Purine alkaloids

Purine alkaloids constitute another important group of alkaloids, present in many stimulantia, such as coffee, tea, mate and cocoa. Examples of these are caffeine, teobromine, and teophylline. Some of these alkaloids have also found medical use. Kurata and coworkers have conducted a number of experiments in which they have demonstrated an increase of alkaloid production in cell cultures of the coffee plant, *Coffea arabica* [68,69], but unfortunately they did not describe their light, and it is not possible to state whether they were dealing with a UV-B effect. Since they used a ferrioxalate actinometer to measure the light, and this is sensitive only to ultraviolet, violet and blue light, it is likely that the light contained a large short-wavelength component. Using callus culture of *C. arabica*, Frischknecht and Baumann [2] also found a very large stimulation of both caffeine and theobromine accumulation. They ascribed the light effect to stress, and did not specify what light they applied. Koshiishi et al. [70] found that caffeine and theobromine are synthesized in tea leaves in both light and darkness, and any small light stimulation that was observed was ascribed to photosynthesis.

6.3. Sterol alkaloids

Bulbs of various species of the genus *Fritillaria*, one of the largest genera within the lily family contain a large number of alkaloids, especially steroid alkaloids (and also other, nitrogen-free steroids) and many of the species have been used for medicinal purposes. Zhang et al. [71], Cao et al. [72], Liu et al. [73] and Zhou et al. [74] describe the chemistry of such substances in various *Fritillaria* species, and Zhang et al. [75] and Yun et al. [76] describe their biological effects. The traditional Chinese medicine zhe bei mu is prepared from the bulbs of *Fritillaria thunbergii*. Li et al. [77] found that the concentration of alkaloids in this plant could be increased by about 50% by UV-B treatment of the plants. The alkaloids were not specified, but the most important alkaloids in this species is are peimine (verticine) and peiminine (verticinone), both with a cevane skeleton. Lime processed bulbs also contain other alkaloids [78].

One case is reported in which there is less of (unidentified) alkaloids in UV-B exposed plants (*Aquilegia caerulea*) in comparison with controls [79].

7. Essential oils and terpenoids

Essential oils constitute a heterogeneous collection of chemical compounds. They have in common that they are synthesized by plants and are volatile and mostly soluble in ethanol. They have traditionally been obtained from plants by extraction and distillation. Since the middle ages, they have been widely used for insecticidal, medicinal and cosmetic purposes. For a detailed review of their biological effects the reader is referred to Bakkali et al. [80]. Schelz et al. [81] have assayed antimicrobial effects of several of them. Some essential oil compounds are terpenoids, i.e. a class of hydrocarbons and derivatives of them. The substances from *Glycyrrhiza* and yew dealt with at the end of this section are also terpenoids.

Karousou et al. [82] studied two different chemotypes of *Mentha spicata*, and found that in one of them UV-B radiation, on a dry weight basis, caused a 50% increase in essential oil production, while in the other chemotype the increase was insignificant.

A more thorough investigation was carried out by Johnson et al. [22] on essential oil production in sweet basil (*Ocimum basilicum* L.), in which the effect of ultraviolet radiation is much greater. They separately analyzed no less than 22 different essential oil compounds in this plant. The effect of UV-B radiation increased with the age of the plants, and was different for different compounds, but mostly positive. At the 5 leaf stage the irradiated plants contained between 3 and 4 times as much of most essential oil components as did the unirradiated control plants. In a later paper [83] by the same group, the authors reported that UV-B radiation is necessary for normal development of oil glands in sweet basil. There seems to be a requirement for UV-B in the filling of the glandular trichomes of this plant.

Roots and rhizomes of licorice (*Glycyrrhiza*, mostly *G. glabra*, *G. uralensis*, *G. inflata*, *G. aspera*, *G. korshinskyi*, *G. eurycarpa*, and *G. glabra*) have been used since at least 500 B.C. for various medical purposes, and are still used in many preparations. It contains various saponins, flavonoids, isoflavones, coumarins, stilbenoids and other compounds. The reader is referred to Asl et al. [84] for a review of the pharmacological effect of these compounds. Licorice, or glycyrrhizin isolated from it, is used as a sweetener. Glycyrrhizin is a triterpenoid saponin that constitutes about 20% of licorice, and has 30–50 times the sweetening power of sucrose.

Afreen et al.[85] found that a three-day treatment of the plants with UV-B increased the contents of glycyrrhizin. In the highest exposure the increase was less than with a lower exposure, but it is difficult to assess the effect, as the description of the UV-B radiation is insufficient, and the treatment time is so short.

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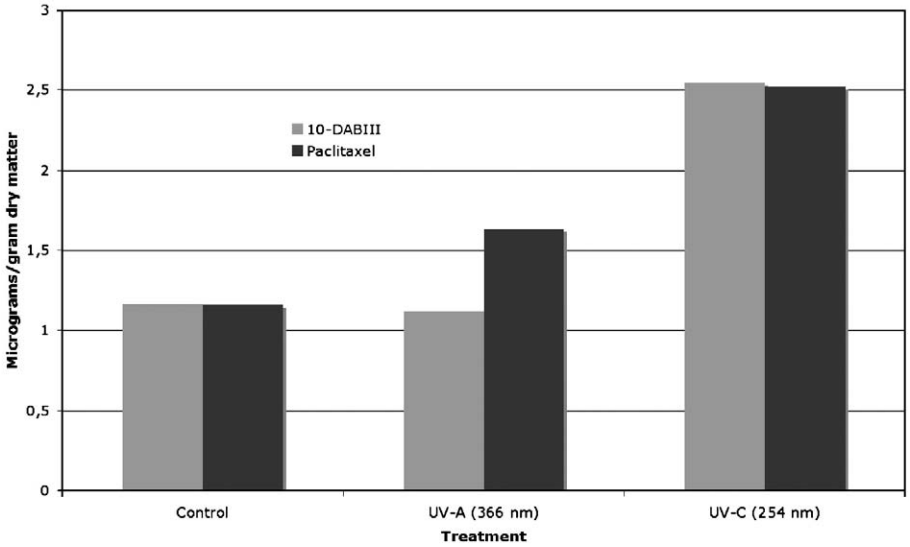

Fig. 6. Effect of ultraviolet radiation on taxoid content in yew twigs. Data from [81].

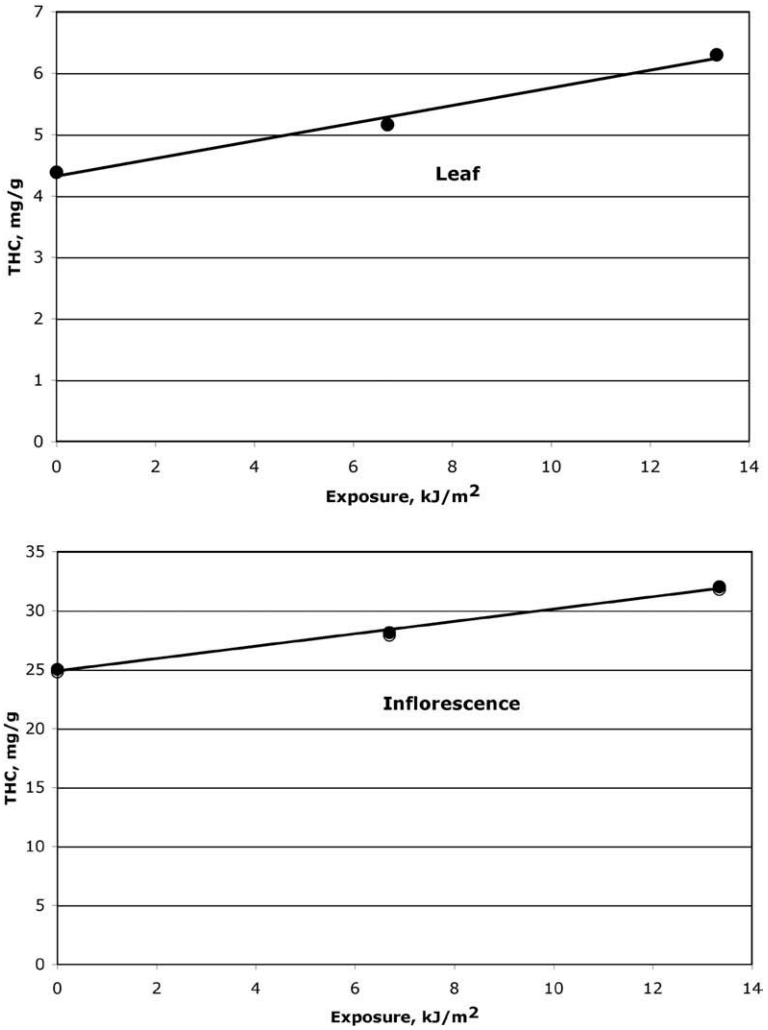

Fig. 7. Accumulation of Δ^9-tetrahydrocannabinol in leaves and floral tissue of *Cannabis sativa*. Vertical bars indicate ± 1 standard error. UV-B_{BE} refers to ultraviolet radiation convoluted with a special action spectrum (weighting function) for plant-active radiation, i.e. before integration over wavelengths the spectral components have been multiplied by this function. This procedure stresses the importance of the short-wavelength components. From [97].

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Yew (*Taxus bacchata*) contains several compounds (terpenoids) collectively referred to as taxoids, which have found use in cancer therapy. They block mitosis by preventing microtubuli depolymerisation. Hajnos et al. [86] studied the effect of ultraviolet radiation on the accumulation of two of them, 10-DAB III and paclitaxel (Fig. 6). During 48 h of irradiation of excised twigs the amounts of both were increased, more by UV-C than by UV-A treatment (UV-B was not tested), but since the radiations were not measured this comparison may be misleading. More of the taxoid taxol accumulated in 2-year old twigs than in 1-year old ones. The effect of the irradiation was much more pronounced for paclitaxel than for 10-DAB III.

Feverfew (*Tanacetum parthenium* [L.] Schultz-Bip., Asteraceae) has been used for 2000 years as a remedy for various medical conditions, including fever, inflammation and migraine. It contains several active substances, including the sesquiterpene lactone parthenolide. Recently parthenolide has received interest for its abilities to modulate intracellular signalling in mammals [87], to inhibit cancer-induced angiogenesis [88] and cell proliferation [89,90], and to induce apoptosis, differentiation [91] or radiation sensitivity [92,93] in various types of cancer cells, although so far few *in vivo* experiments have been carried out. In feverfew plants exposed to water stress, but not in well-watered ones, ultraviolet (UV-A + UV-B) radiation increases the accumulation of parthenolide up to about three times the control [94].

8. Cannabinoids

Pate [95] cites older literature suggesting that UV-B radiation promotes cannaboid production in *Cannabis* and also speculates about cannaboid evolution. Plots of estimated UV-B exposure in different growth places shows an increase in Δ^9-tetrahydrocannabinol (Δ^9-THC) with exposure, but a decrease in cannabidiol. Lydon [96] and Lydon et al.[97] found that in both leaf and floral tissues the concentration of Δ^9-THC but not of other cannabinoids increased linearly with UV-B exposure in drug-type *Cannabis sativa* plants (Fig. 7), but not in fiber-type plants of the same species. Nowadays many sites on the Internet show that the dependency of cannabinol accumulation on UV-B radiation is common knowledge among private entrepreneurs in the drug industry. The biosynthetic pathway of cannabinoid synthesis is shown in Fig. 8.

It is not known which enzyme or enzymes for Δ^9-tetrahydrocannabinol biosynthesis are induced or stimulated by UV-B radiation, but one can speculate. The gene for polyketide synthase catalyzing the synthesis of olivetolic acid possesses strong sequence homology with chalcone synthase and may have evolved from this. Chalcone synthase is one of the classic UV-B-regulated enzymes.

9. Glucosinolates and isothiocyanates

Glucosinolates are sulfur-rich, anionic natural products that upon hydrolysis by endogenous thioglucosidases called myrosinases produce, among other compounds, isothiocyanates [98,99]. The myrosinases occur in cruciferous plants in compartments separate from those containing the glucosinolates. The two compounds come in contact when animals eat from the plant, and the isothiocyanates ("mustard oils") produced act as deterrants on most animals, but attract some specialists. Some glucosinolate-producing plants have been used as medicinal plants [100], and recently isothiocyanates have gained interest as cytostatica and cytotoxins in cancer therapy [101-103]. Both glucosinolate content and myrosinase activity are increased by UV-B radiation in some plants [104]. In *Nasturtium officinale* the UV-B effect on glucosinolate content was much greater in old leaves than in young ones, and in *Sinapis alba* the effect on myrosinase activity was greatest for the insoluble fraction, and also greater for old leaves than for young ones.

10. *Hypericum* substances

Several species of *Hypericum* (St. John's wort) are used as medicinal plants, and *H. perforatum* is grown commercially. Several secondary metabolites are considered to be of medical value, including pseudohypericin, hypericin, hyperforin, adhyperforin, chlorogenic acid, rutin, hyperoside, isoquercitin, quercitin, xanthones, flavonoids and tannins. Brechner [24] investigated the effects of several environmental factors on the contents of hypericin, pseudohypericin (hydroxyhypericin) and hyperforin. A pulse of less than an hour of UV-B radiation (10 μmol m^{-2} s^{-1}, with traces of UV-C) caused a transient increase of all three compounds. In field-grown plants (with natural UV-B) there was less of the compounds than in greenhouse-grown ones, but this difference cannot be ascribed to UV-B.

11. Compounds acting as human hormones

11.1. Melatonin

Melatonin is a hormone of importance for normal diurnal rhythmicity. It is accumulated in various plant parts, particularly in some seeds. Its accumulation is affected by the light conditions under which the plants grow. In *Glycyrrhiza uralensis* the accumulation in the root (the part of the plant which is used for human consumption; see above) is rapidly increased many times by the exposure of the shoot to UV-B radiation [105]. In three month old control plants these researchers found 12 μg g^{-1} of root tissue. In similarly grown plants exposed for three days and 16 h per day to 1.13 W m^{-2} of UV-B radiation the content was 71 μg g^{-1}. The spectral composition of the UV-B radiation was not described, and there may have been traces of UV-C radiation (in addition to UV-A and visible light), since no use of filters between lamp and plants was mentioned.

11.2. Vitamin D

Vitamin D is undoubtedly the most well known health-promoting chemical whose synthesis depends on ultraviolet radiation. We can form it ourselves on our skin, and so it is not a vitamin in a strict sense, but we can also ingest it with food. In both cases the synthesis occurs under the influence of ultraviolet radiation (naturally UV-B, artificially UV-C can also be used). The vitamin D that we ingest is mostly formed in plankton that is exposed to UV-B and then ingested by fish, and the richest source is the liver of some fishes, for instance cod. Vitamin D was discovered because it is needed for the

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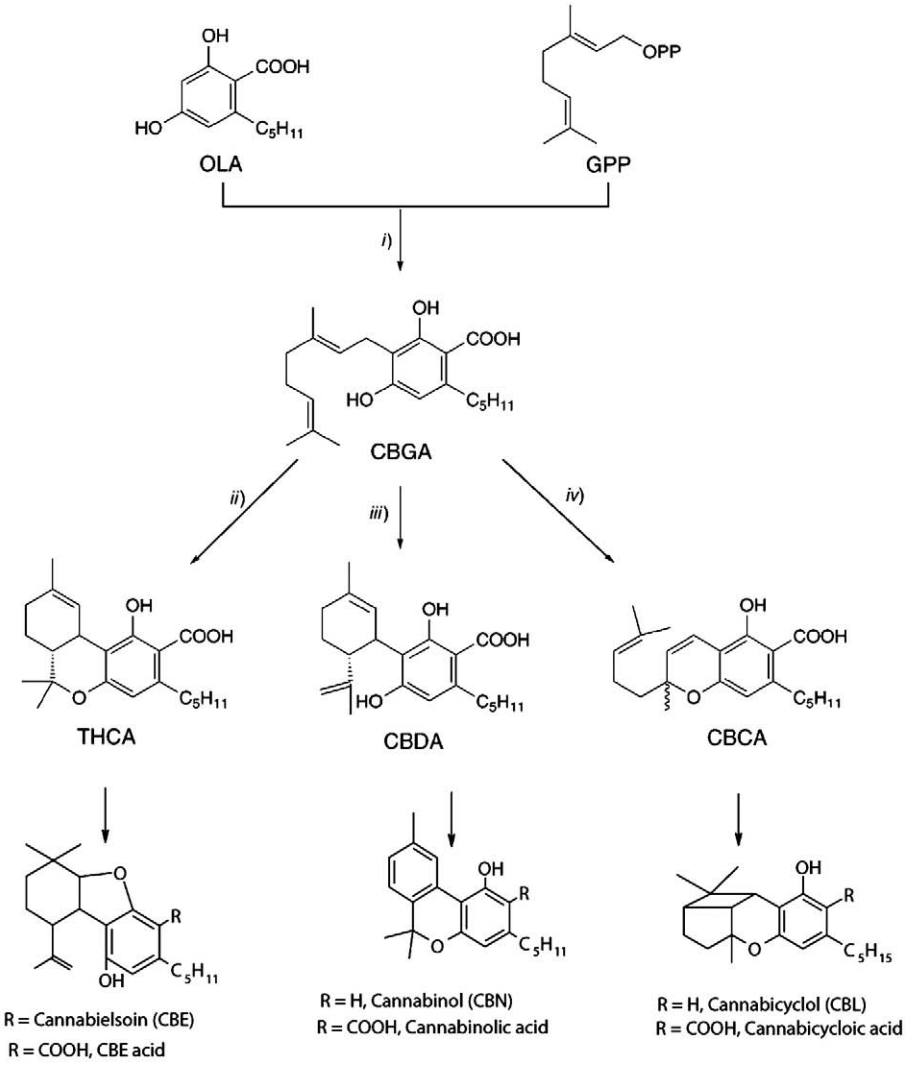

Fig. 8. Biosynthesis pathways of cannabinoids in *Cannabis sativa*. OLA, olivetolic acid; THCA, Δ^9-tetrahydrocannabinolic acid. Adapted from Raharjo TJ, Chang W-T, Verberne MC, Peltenburg-Looman AMG, Linthorst HJM, Verpoorte R. Plant Physiology and Biochemistry 2004:42: 291 and Taura F, Sirikantaramas S, Shoyama Yoshinari, Shoyama Yukihiro, Morimoto S. Chem. Biodiversity 2007: 4: 1649.

normal development of our skeletons (severe deficiency in childhood leads to rickets), but later it has been discovered that it is important for a great number of other processes in our bodies and protects from a number of diseases. Vitamin D is doubly hydroxylated in the human and animal body to form the active hormone 1α,25-dihydroxyvitamin D. For reviews of this the reader is referred to Björn [106] and the literature cited therein.

There are (at least) two kinds of vitamin D, called vitamin D_2 and vitamin D_3. (Vitamin D_1 does not exist, so the numbering depends on a mistake.) Due to another mistake, vitamin D_2 is sometimes referred to as "plant vitamin D" and vitamin D_3 as "animal vitamin D". The truth is that plants as well as some algae form both vitamin D_2 and vitamin D_3 upon UV-B (or UV-C) irradiation. The substance that we produce ourselves in our bodies is vitamin D_3, as is also the substance obtainable from fish liver and generally supplied as medicine. Why phytoplankton at the base of the marine food-chain produce both vitamin forms, but only the D_3 form is found in fish liver has never been investigated.

Vitamin D differs from all the other medicinals in this article in that neither genes nor enzymes are involved in the action of ultraviolet radiation. The role of UV is to drive a completely photochemical conversion of provitamin D to an intermediate called previtamin D. After this there follows a thermochemical isomerization to vitamin D. Each of these compounds exist in a D_2 and a D_3 form. For further details concerning the ecology and photobiology of vitamin D, see Björn [106] and the literature cited therein. What we would like to stress here is that a large part of the population in many countries is vitamin D deficient or at least insufficient.

Hess and Weinstock [107] have already shown that exposure of lettuce and several other foodstuffs to UV radiation would make them useful for preventing rickets. These early workers used UV-C radiation, but later it has been shown several times that UV-B exposure of plant leaves causes the

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accumulation of both vitamin D_2 and vitamin D_3 in them [108,109]. A few plants in the Solanaceae (potato family) are able to form very large amounts of these vitamins and their hydroxylated derivatives even without UV-B or other light [110].

The major sterol in membranes of fungal cells is ergosterol = provitamin D_2, so if fungi are exposed to ultraviolet (B or C) radiation, vitamin D_2 is formed via previtamin D_2, and there exists a large literature on this vitamin D_2 formation and the medical uses thereof [111–113]. When ergosterol or vitamin D_2, but no corresponding D_3, forms are found in plant material, it may be due to fungal contamination or fungal endophytes [114]. Reindeer lichen contains both vitamins D_2 and D_3, and more when growing at low than at high latitude, which indicates a correlation with UV-B exposure [115].

11.3. Phytoestrogens

Phytoestrogens (also called plant estrogens) are substances produced by plants which in mammals elicit effects of the same kind as the mammal estrogen (oestrogen) hormones: estradiol, estriol, and estrone. The existence of such substances was discovered when it was shown that breeding problems of Australian sheep could be traced to their grazing of subterranean clover [116]. Whether phytoestrogens have evolved as protection against grazing animals, or the effect on mammal reproduction is fortuitous is uncertain.

There are two different estrogen receptors in the human body, ERα and ERβ. It may happen that one phytoestrogen binds more strongly to ERα than to ERβ, while the reverse is true for another phytoestrogen, and there is therefore no unambiguous ranking of estrogenic potency for different substances. Some substances produced by plants do not themselves bind to a phytoestrogen receptor, but are in the animal or human body transformed to estrogens. Various kinds of both natural substances and environmental pollutants may have estrogenic effects. Isoflavones often exhibit a very strong activity, and many flavonoids (see Section Flavonoids and Fig. 1 above) weaker activity, and plants also produce steroids with estrogen activity. Some researchers regard resveratrol (mentioned in Section 4. Stilbenes above) as a phytoestrogen [117,118], but this opinion is controversial.

One of the most potent and most studied phytoestrogens is the isoflavon genistein [119], which occurs in plants both in the free form, but in greater amounts as glycosides, which are hydrolyzed upon ingestion by mammals. In leguminous plants (family Papilionideae) it is constitutive, but the accumulation is stimulated (in some cases doubled) by UV-B radiation [120]. The isoflavonoid synthase gene can be transferred from soybean to plants of other families, such as *Arabidopsis thaliana* (family Brassicaceae), and they can then also produce ginestein [121,122] in some cases after further genetic manipulation. Also in such transformed plants ginestein content can be increased by UV-B radiation.

Phytoestrogens can have both beneficial and damaging effects on human health [123]. Some plant substances resemble human estrogens sufficiently to bind to the receptor, but do not have estrogen activity, but rather outcompete the estrogens and prevent their effect; i.e. they act as anti-estrogens [124].

12. Why is the biosynthesis of some secondary metabolites stimulated by UV-B radiation?

One can think of several possible answers to the question in the heading:

1. It is a general stress response, and the biological function may be to protect the plant from herbivory or parasites. This would be particularly likely if the response is the same if the plant is wounded, attacked by insects, or exposed to fungal elicitors.
2. The secondary metabolites have a sunscreening effect and protect cells from the radiation. This would be especially likely if the metabolites are concentrated to the epidermis or other superficial tissues.
3. The radiation aids in reaching a certain level of general differentiation necessary for production of secondary metabolites.

We can probably find examples of all these cases. Flavonoids frequently have a clear role as sunscreens and protectants against photoproduced ROS. Even if they occur in different kinds of cells and cell compartments, a large part of the UV-B inducible fraction is often localized to the epidermis of leaves and other aerial organs.

Alkaloids, on the other hand, are not only UV-B absorbing, but also mostly very toxic. Even if they sometimes are located near the plant surface, this in no way speaks against their role as deterrants against herbivores and parasites. Levin [125] noted that the percentage of alkaloid-containing plants in the flora increases towards the equator, but this cannot be ascribed to a radiation protective role without further evidence. Although nicotine can be induced in tobacco callus culture by UV-B [126] and has a high absorbing power (absorption coefficient) in the ultraviolet region, Baldwin and Huh [127] could not demonstrate any radiation protection by nicotine when its concentration was artificially elevated in *Datura stramonium* plants. In this experiment nicotine content was increased in the leaves, but whether it accumulated in the epidermis or deep in the leaves is not known.

Essential oils are mostly produced by glandular hairs and other surface structures, and often have a clear role in chemical communication with pollinators and other animals useful to the plant. In this case possibility 3 above appears plausible. A general discussion of localization of secondary metabolites can be found in Kutchan [128], Kutchan and Dixon [129].

A clear case of a secondary metabolite which does not act as a UV protectant is the accumulation of melatonin in the root of *Glycyrrhiza* when the shoot is exposed to UV. In this case it is likely that we are dealing with a stress response.

13. Conclusion

We have seen that the contents of medicinal substances of many kinds in many plants are increased by exposure to ultraviolet radiation, and in particular UV-B radiation. This effect is not always regarded as a stress phenomenon, as in many cases the increase in the secondary metabolites can be achieved by radiation so low that they do not negatively affect growth, and do not result in any visible damage. Thus, in order to make the production of medicinal plant substances efficient, it may be advisable to try exposure to ultraviolet radiation also in cases which have not yet been investigated. In

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some cases UV-A or UV-C radiation may be more suitable than UV-B.

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