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The metabolites of dietary chlorophylls

Lifu Ma[1], David Dolphin*

Department of Chemistry, 2036 Main Mall, University of British Columbia, Vancouver, BC, Canada V6T 1Z1

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Abstract

Chlorophylls, the green pigments responsible for photosynthesis in plants, algae and bacteria, are also part of the daily diet of herbivorous feeders. Numerous metabolic derivatives of the major green pigment, chlorophyll-*a*, have been found in a wide variety of organisms during the last decade. Studies of these metabolites show that some are antioxidants or cellular signaling mediators in vivo. The metabolites of bacteriochlorophylls-*c* and *d*, recently found in the deep-sea dragon fish, *Malacosteus niger*, function as a visual photosensitizer, enabling the fish to seek their prey in 'the dark'. Discovery of these metabolites as well as their interesting biological functions raises questions as to the roles of chlorophyll derivatives in the chemical ecology of herbivorous life forms. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Keywords: Chlorophyll; Diet; Metabolism; Antioxidant; Cell signaling; Photosensitizer

1. Introduction

As the pigments responsible for the characteristic color of green plants, algae and bacteria, chlorophylls are best known as energy transducers that capture sunlight for the production of oxygen and sugars, thereby establishing the foundation for animal food chains (Fajer, 1991). They are also part of dietary components from edible leaves and algae found in abundance in nutrients and micronutrients (Committee on Diet, 1982) that are necessary for our well-being and have been suggested as having protective properties in the prevention of coronary heart disease (Gordon, 1996), certain cancers (Murakami, Ohigashi, & Koshimizu, 1996; Kitts, 1997), diabetes (Hari, Patel, & Martin, 1994) and cataracts (Bringham, Atkinson, Liggins, Bluck, & Coward, 1998). For humans, green leafy vegetables have long been considered especially healthful, both physically and even spiritually.

The contents of chlorophylls in green vegetables are high: for example, spinach contains as much as 1% chlorophylls on a dry-weight basis (Chipchase, 1961). Swiss chard, bok choy (a Chinese cabbage), collards, parsley and dandelion greens, to name but a few, are also rich in chlorophylls. Vegetable extracts containing chlorophylls have been found to be antimutagenic (Lai, Butler, & Matney, 1980; Terwel & van der Hoeven, 1985) and anticarcinogenic (Negishi, Rai, & Hayatsu, 1997) in vitro and in vivo. Chlorophyllin, a saponified mixture of chlorophyll extracts, has been widely used in oral hygiene such as chewing gums, toothpastes and in the medicinal industry as a treatment for anemia and hypertension (Kephart, 1955). A copper complex of chlorophyllin has also been reported as an antioxidant in rat liver homogenates (Sato et al., 1986). The high content as well as the widespread presence of chlorophylls in a variety of foods and beverages raise questions about their possible nutrient and health effects. Unfortunately, little is known to date and, indeed, few attempts to establish a connection between dietary chlorophylls and their health and metabolic impact have been reported.

On the other hand, the search for new tetrapyrrolic structures in a variety of marine and terrestrial herbivores during the last decade has brought about the discovery of many new chlorophyll metabolites. Studies of these metabolites have shown that some organisms have manipulated dietary chlorophylls for unique biological functions and/or beneficial effects. In contrast to chlorophyll breakdown in plants, where a rapid

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* Corresponding author. Tel.: +1-604-822-4571; Fax: +1-604-822-9678; E-mail: david@dolphin.chem.ubc.ca.

[1] Present address: Howard Hughes Medical Institute, Department of Chemistry, University of California, Berkeley, CA 94720, USA.

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degradation of the green pigments to colorless 'non-fluorescent' linear tetrapyrroles occurs in senescent leaves (Bortlik, Peisker, & Matile, 1990; Kräutler, Jaun, Bortlik, Schellenberg, & Matile, 1991), the metabolism of chlorophylls in other organisms may embody a series of relatively mild chemical events, so that the tetrapyrrolic macrocycle essentially remains intact. However, compared with most other dietary phytochemicals, which have relatively lower chemical reactivity, chlorophylls may be very susceptible to digestive modifications, particularly at the peripheral groups of the macrocycle. Therefore, from the viewpoint of chemical ecology as well as of public health, the metabolism of dietary chlorophylls merits further research.

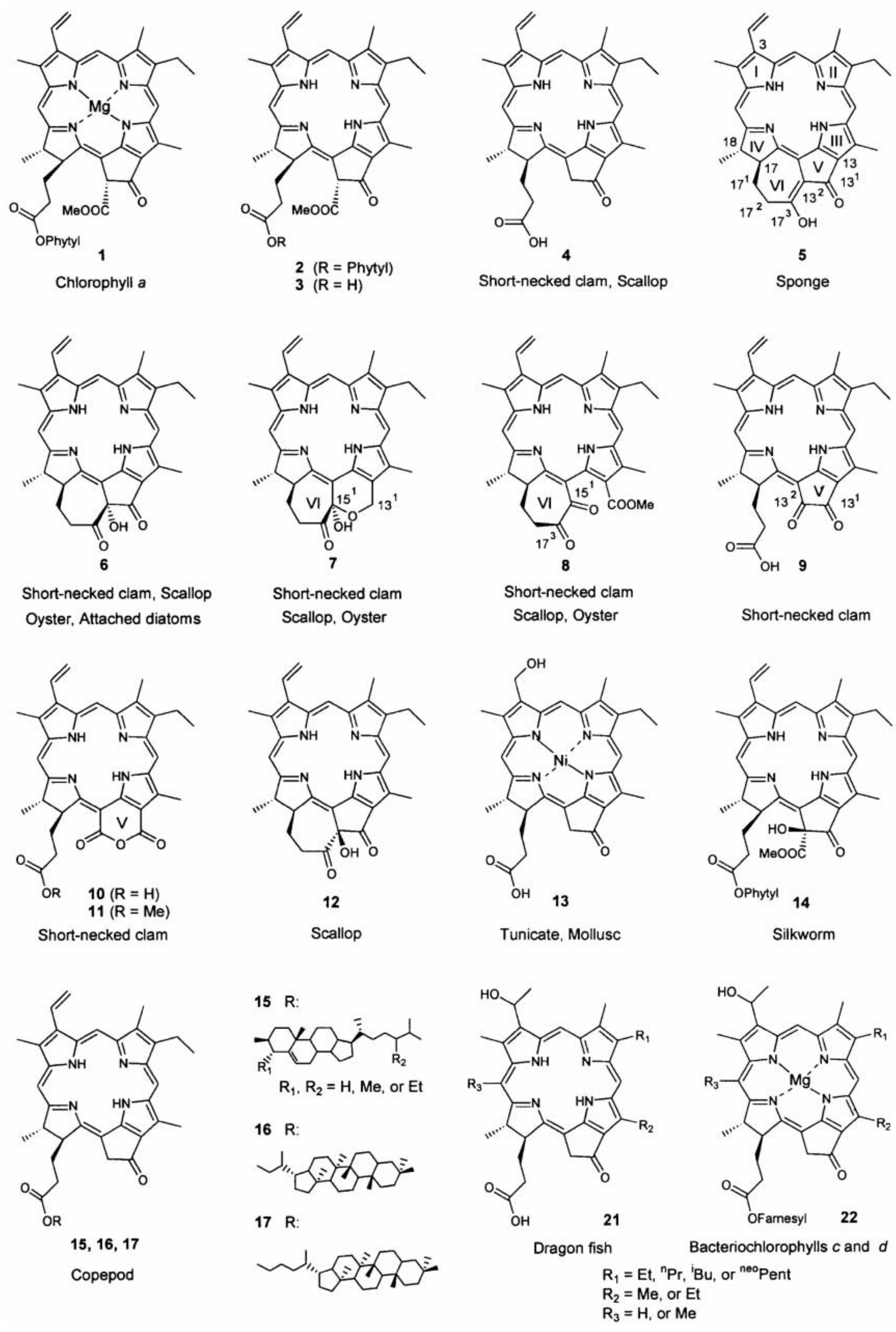
It is the intention of this contribution to describe the present status of this area and to indicate the gaps in our knowledge. We focus only on those metabolic products of dietary chlorophylls that have been found to play biological functions in vivo. Additional areas addressed are the inherent chemical nature, possible functional mechanisms, and biogenesis of these metabolites.

2. Chlorophyll-*a* metabolites as natural antioxidants

Chemically, chlorophylls are a group of magnesium-metallated tetrapyrroles related to porphyrins but containing a characteristic fifth isocyclic ring and a long-chain isoprenoid alcohol group (e.g. phytol, farnesol, etc.). Chlorophyll-*a* (**1**), the most abundant and most important chlorophyll of the family, represents about 75% of the green pigments in plants, but may be even higher in concentration in certain algae, some of which (e.g. blue–green algae) contain only chlorophyll-*a* (Scheer, 1991). It is extremely sensitive to various modification reactions (Hynninen, 1991) such as demetallation and photooxidation and, clearly, is susceptible to metabolic modification in vivo. Indeed, considerable quantities of chlorophyll-*a* pass into the guts of terrestrial herbivores and aquatic grazers. Little, if any, chlorophyll-*a* emerges intact. The most common extracts isolated from these species are the demetallated chlorophyll-*a* (pheophytin-*a*, **2**), pheophorbide-*a* (**3**) (loss of the phytol group), and under harsher conditions, the decarboxylated product (pyropheophorbide-*a*, **4**). These derivatives are also the staging points for literally dozens of subsequent chemical transformation products in the laboratory (Hynninen, 1991; Goodwin, 1965). However, most metabolites recently reported from dietary chlorophyll-*a* have novel and unique structures and are significantly different from the known degradative products of chlorophyll-*a*. A striking feature in this class are chemical modifications substantially around the southern half of the molecule and in most cases the appearance of an additional exocyclic ring (ring VI) in the chlorin framework. Of this family of metabolites, $13^2,17^3$-cyclopheophorbide-*a* enol (**5**) was the first to be isolated from the sponge *Darwinella oxeata* in 1986 (Karuso et al., 1986). As revealed by single crystal X-ray crystallography, chlorin **5** has an additional exocyclic ring VI and exists only in the enolic form. Its biological function remained unknown until the closely related 13^2S-hydroxychlorophyllone *a* (**6**) ('*S*' or '*R*' denotes the absolute configuration at C-13^2 or C-15^1 position where appropriate) was found in 1990 as an antioxidant in the short-necked clam, *Ruditapes philippinarum,* which occurs in the Hamana lake, Shizuoka Prefecture, Japan (Sakata et al., 1990).

The antioxidative activity of this chlorin was discovered as a result of studies on the peroxide value (POV, which is an index of free radical-mediated oxidative damage in lipids) and mutagenicity among the extracts of various marine species that contain large amounts of highly unsaturated fatty acids (the most readily oxidized lipids), such as various kinds of marine fish, bivalves and attached and wafting diatoms (Takao, Kitatani, Watanabe, Yagi, & Sakata, 1994). However, instead of the expected high POV (larger than 100 meq/per kg extracts) usually found in the extract, much lower POV (less than 10 meq/per kg extracts) were found, suggesting the existence of strong antioxidants in these organisms. Further screening of these extracts revealed the presence of new antioxidative chlorins, 13^2S-hydroxychlorophyllone-*a* (**6**), 15^1R-hydroxychlorophyllonelactone-*a* (**7**), chlorophyllonic acid *a* methyl ester (**8**), 13^2-oxopyropheophorbide-*a* (**9**), as well as the known chlorins, pyropheophorbide-*a* (**4**), purpurin 18 (**10**) and purpurin 18 methyl ester (**11**) in the edible parts of the short-necked clam (Watanabe et al., 1993). 13^2R-Hydroxychlorophyllone-*a* (**12**), an epimer of **6**, together with **7**, **8** and **4** occur in the viscera of the scallop, *Patinopecten yessoensis*. The presence of **6**, **7** and **8** in the viscera of the oyster *Crassostrea* sp. and **6** in the mixture of attached diatoms (*Fragilaria oceanica*, *F. cylindus*, *Nitzschia closterium*, *N. seriata*, *Cocconeis pseudomariginata*, *Hyalodiscus stelliger*) cultured for seedling production of juvenile abalone was also confirmed (Sakata, Yamamoto, & Watanabe, 1994). A detailed description of their structures and their principal sources is shown in Scheme 1.

These chlorins, isolated by classical solvent (CH_3Cl/MeOH) extraction procedures, were found to have higher antioxidative activity at a dose of 3 μg than that of 20 μg of α-tocophenol in the dark (Sakata et al., 1994), confirming that they are the main antioxidants in these species. Their structural identities were elucidated by single crystal X-ray crystallography (Karuso et al., 1986; Yamamoto et al., 1992), UV–


1
Chlorophyll a
Mg
MeOOC
OPhytyl
2 (R = Phytyl)
3 (R = H)
OR
4
Short-necked clam, Scallop
OH
5
Sponge
I
II
III
IV
V
VI
3
13
13¹
13²
17
17¹
17²
17³
18
6
Short-necked clam, Scallop
Oyster, Attached diatoms
7
Short-necked clam
Scallop, Oyster
15¹
8
Short-necked clam
Scallop, Oyster
COOMe
9
Short-necked clam
10 (R = H)
11 (R = Me)
Short-necked clam
12
Scallop
13
Tunicate, Mollusc
Ni
14
Silkworm
HO
15, 16, 17
Copepod
15 R:
R₁, R₂ = H, Me, or Et
16 R:
17 R:
21
Dragon fish
22
Bacteriochlorophylls c and d
OFarnesyl
R₁ = Et, ⁿPr, ⁱBu, or ⁿᵉᵒPent
R₂ = Me, or Et
R₃ = H, or Me

Scheme 1.

VIS, MS, and ^{1}H and ^{13}C NMR spectroscopies, and further verified by a partial synthesis (Ma & Dolphin, 1996a) from chlorophyll-*a*.

3. Other chlorophyll-*a* metabolites

In addition to the southern half of chlorophyll-*a*, metabolism also takes place on other susceptible moieties within the molecule such as the 3-vinyl group. The nickel-containing tunichlorin (3-hydroxymethylpyropheophorbide-*a*, **13**) was initially discovered by Rihehart, Kishore, Bible, Sakai, Sullins and Li, 1988 and Rihehart et al. (1988) in the tunicate *Trididemnum solidum*, which occurs in the Caribbean Sea and subsequently found in the Papua New Guinea shell-less mollusc *Dlabella auricularia* in 1993 (Pettit, Kantoci, Doubek, & Tucker, 1993). Structural elucidation was carried out by standard spectroscopic methods on dimethyltunichlorin, which was prepared by etherification of the 3-hydroxymethyl group and esterification of the 17-propionic acid side chain. Dimethyltunichlorin synthesized from tunichlorin is in all respects identical to dimethyltunichlorin prepared from chlorophyll-*a* by partial synthesis. Discovery of tunichlorin in the sea hare and the tunicate suggests that its occurrence in algae-consuming marine animals may be more common than earlier realized, and it may represent an important step toward understanding the role of nickel in marine animal metabolism. Tunichlorin appears as an ideal accumulator of nickel although its biological function needs to be further investigated. Other known natural nickel-chelated tetrapyrroles (Stolzenberg & Stershic, 1988) include coenzyme F_{430}, the prosthetic group of methyl-coenzyme M reductases and petroporphyrins (Callot, 1991; 'molecular fossils') found in petroleums and in a wide variety of sediments.

In most animals the acidic environment of the stomach would be expected to bring about loss of Mg and the phytol group of chlorophyll-*a* to produce pheophorbide-*a*. However, in certain cases, the phytyl ester group remains intact even after the digestive processes. For example, 13^2*S*-hydroxypheophytin-*a* (**14**) (Dai et al., 1992) was isolated from *Silkworm excreta*, which has a long history of use as a folk medicine in the Far East (Zhang, Hong, & Liu, 1988). Recent studies indicated that chlorin **14** possesses a high quantum efficiency ($>50\%$) for the photosensitized production of singlet oxygen, suggesting that it has a potential as a drug for photodynamic therapy of tumors (Dai et al., 1992). It seems certain that **14** is a dietary metabolite of chlorophyll-*a*, because extracts of mulberry and spinach leaves have been shown to lack **14** (Dai et al., 1992). Furthermore, compound **14** is a unique metabolic product of silkworm and has not been reported from other sources. Although the phytyl ester survives the digestive process, specific oxidation of pheophytin-*a* at the C-13^2 position to provide the unique 13^2*S* hydroxyl epimer, takes place, indicativety an enzymatic modification.

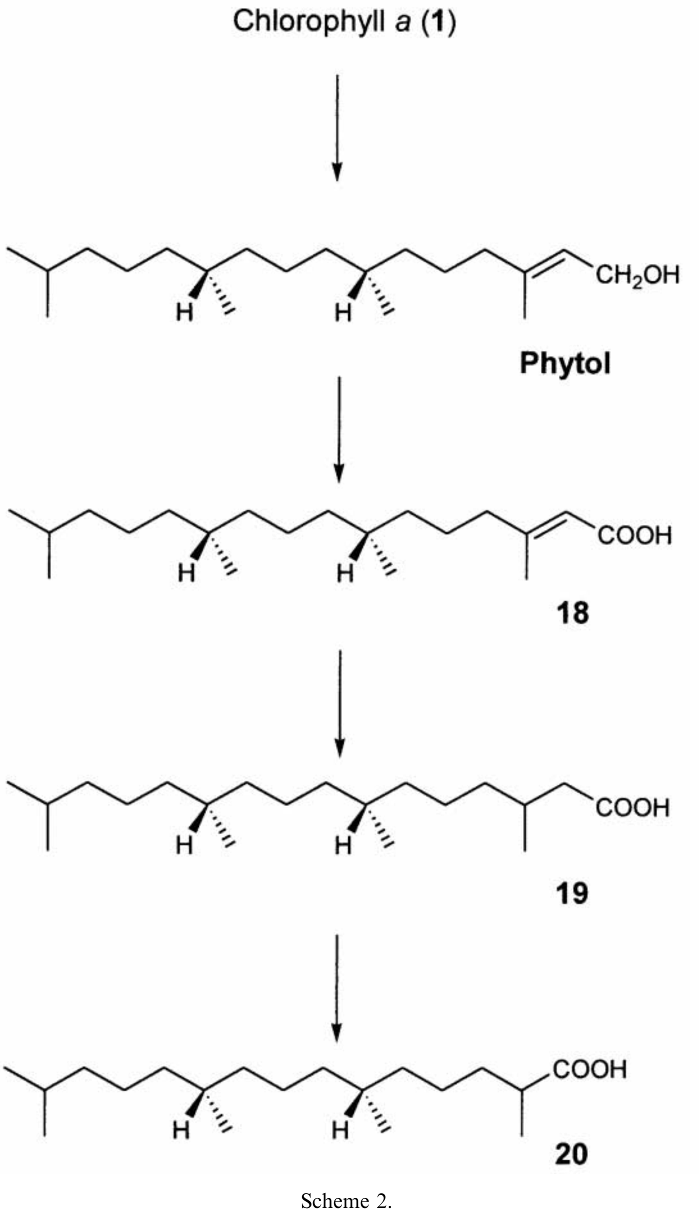
Phytol is the most common esterifying alcohol of chlorophylls. However, the discovery of chlorophyll metabolites carrying an alcohol other than phytol at the C-17^3 position complicates the metabolic processes involved. Lake Valencia, in Venezuela, is a highly eutrophic lake with a great variety of cyanobacteria. These blue–green algae contain solely chlorophyll-*a* as the light harvesting pigment and a variety of sterols (Ourisson, Albrecht, & Rohmer, 1979). Several steryl chlorin esters occur ubiquitously in the surface sediment (less than 55 cm deep) within the lake and have been characterized by HPLC–MS (or GC–MS) and by partial synthesis from chlorophyll-*a* (King & Repeta, 1991; Echardt et al., 1992; Harradine, Peakman, & Maxwell, 1996b). The macrocyclic ring was found to be exclusively pyropheophorbide-*a* (**4**) and the esterifying alcohols were cholesterol (**15**) (King & Repeta, 1991), dihomohopanol (**16**) (Harradine et al., 1996b) and tetrahymanol (**17**) (Harradine et al., 1996b) (Fig. 1). Recent work has shown their formation to occur during herbivory of a marine diatom by a copepod (Harradine, Harris, Head, Harris, & Maxwell, 1996a), a smaller relative of crabs and lobsters. Since the formation of steryl chlorin esters has been demonstrated to occur with 48 h during zooplankton grazing, it is unclear whether the esterification occurs specifically with digested chlorophyll or with ingested chlorophyll present in the zooplankton gut from a mixed phytoplanktonic diet.

4. Phytol metabolites as cellular signaling mediators

The specific esterification of steryl chlorins undoubtedly points to the biological significance of these species, but this is still poorly understood on the molecular scale, as is the variability of esterifying alcohols within the bacteriochlorophylls from different bacteria (Katz et al., 1972). Phytol contains more than one third of all carbon atoms of chlorophyll and its metabolites, particularly phytenic acid (**18**) and phytanic acid (**19**) have also been recently isolated from bovine serum (Kitareewan et al., 1996). These metabolites are believed to mediate cell signaling, by functioning as lipophilic ligands, similar to steroidal hormones and to bind and activate nuclear receptors that regulate gene expression in vivo. Previously, 9-*cis*-retinoic acid was defined as a potent activator of the nuclear receptor RXR, which plays a central role in cell signaling by pairing with a host of other receptors (Koelle et al., 1991). Recent studies have shown that phytol metabolites, phytenic acid, phytanic acid and pristanic acid (**20**) (Scheme 2), are compelling candidates for physiological effectors, because their RXR binding affinities and activation potencies match their micromolar circulating concentrations. Phytol metabolites in animal tissues are exclusively derived from dietary chlorophyll via a possible pathway (Steinberg, 1983) as shown in Fig. 2. First, the phytol ester is hydrolyzed, which is followed by oxidation to phytenic acid (**18**). Phytenic acid is then reduced to phytanic acid (**19**), which after hydroxylation and subsequent oxidation would give pristanic acid (**20**). Pristanic acid is finally metabolized by fatty acid β-oxidation pathways (Lough, 1977). Given their extensive dietary origin, these chlorophyll metabolites may represent essential nutrients that coordinate cellular metabolism through RXR-dependent signaling pathways.

5. Metabolites of bacteriochlorophylls as visual photosensitizer

In addition to the metabolites and biological functions described above, the most fascinating function of chlorophyll metabolites identified to date appears from the bacteriochlorophyll metabolites (**21**), which were very recently found in the predatory deep-sea dragon fish, *Malacosteus niger* (Douglas et al., 1998). *M. niger* is known to emit far-red light from suborbital photophores. This rare red bioluminescence serves as a 'sniper scope' that lets the black, toothy fish illuminate its



Scheme 2.

prey and communicate with other members in its family without being seen by other deep-sea animals. Recent studies by Douglas et al. (1998) have shown that this unusual long-wavelength sensitivity of *M. niger* is due to the presence of an additional retinal pigment with an absorption peak at 667 nm. When the pigment absorbs red light it triggers a visual signal just as the fish's visual pigments do when they absorb shorter wavelengths of light. The pigment thus acts as a phototransducer.

From the photosensitizer's UV–VIS absorption, mass and fluorescence excitation and emission spectra, it was determined that this pigment (**21**) is essentially a magnesium- and farnesol-free mixture of bateriochlorophylls-*c* and *d* (**22**), the chlorophylls present in bacterial strains such as *Chlorobium*, a green unicellular organism. Bacterichlorophylls generally occur as a mixture of homologues and are the known dietary source of copepods (small crustaceans). It is likely that photosensitizer **21** in *M. niger* derives from a diet of these copepods (Zurer, 1998).

6. Hypothetical metabolic pathways

It is interesting to note that none of the known dietary chlorophyll metabolites have structures similar to those derived from chlorophyll allomerization (autooxidation) (Hynninen, 1991; Brereton, Rahmani, Liang, & Kvalheim, 1994), suggesting that chlorophylls are digested in nonbasic (nonnucleophilic) and/or anaerobic conditions. How the series of metabolic reactions of chlorophyll-*a* (e.g. metallation and hydroxylation) occur in vivo remains to be investigated. Many enzymes, which mimic the synthetic transformations of these metabolic chlorins from chlorophyll-*a*, have been found in nature. Enzymes responsible for the removal of the central chelated magnesium ion, so-called magnesium dechelatases, have been reported on a number of occasions (Langmeier, Ginsburg, & Matile, 1993). However, none of the systems investigated in the past has been fully characterized, partly because of the difficulty of distinguishing endogeneous enzymatic demetallation from artifacts. It may be anticipated that loss of the magnesium atom precedes the oxidative hydroxylation of the macrocycle at the C-13^2 position in the enzymatic degradation. More recently, an enzyme catalyzing the conversion of pheophorbide-*a* to a pyropheophobide-*a* precursor has been found in the soluble protein fraction of *Chenopodium alba* (Shoio, Watanabe, Tomita, Tsuchiya, & Takamiya, 1995). The precursor was subsequently converted nonenzymatically to pyropheophorbide-*a*. Enzymatic transformation of chlorophyll-*a* to pyropheophorbide-*a* has also been confirmed in a mutant strain of the microalga, *Chlorella fusca* (Ziegler, Blaheta, Guha, & Schonegge, 1988). The assumed biosynthetic origin of 13^2,17^3-cyclopheophorbide-*a* enol (**5**), via an intramolecular Claisen-type condensation of pyropheophorbide-*a* (**4**), is supported by the facile chemical transformation (Falk, Hoornaert, Isenring, & Eschenmoser, 1975; Ma & Dolphin, 1995). Actually, only pyropheophorbide-*a* and its esters (not their metallated compounds) can participate in this cyclization reaction. Our attempts to extend this reaction to chlorophyll-*a* and its closely related derivatives, pheophytin-*a* (**2**) and pheophorbide-*a* methyl ester, were unsuccessful (Ma & Dolphin, 1996a).

The enzymatic oxidation of 13^2,17^3-cyclopheophorbide-*a* enol (**5**) to give hydroxychlorins **6** and **12** has been supported by an asymmetric hydroxylation (Ma & Dolphin, 1995). Periodate oxidation (Ma & Dolphin, 1996a; Ma & Dolphin, 1996b) of either epimer of **6** or **12**, was found to give similar products, i.e. a mixture of mono- and di-oxidized products **7**, **9** and **10**, which coincidentally parallels all the antioxidative chlorins isolated from the short-necked clam, *R. philippinarum*. This observation suggests that **7**, **9** and **10** were probably biosynthesized by 'periodate type' oxidation of **6**. In fact, flavin-dependent monooxygenases have been identified which catalyze oxidation of acyclic and alicyclic hydroxyketones to hydroxylactones in soil bacteria (Walsh & Chen, 1988). However, the natural oxidation of hydroxychlorin **12** is highly regioselective in the scallop, *Pactinopecten yessoensis*, which only metabolizes the mono-oxidized products of the exocyclic ring V, hydroxylactone **7** and its methyl ester **8**. Thus, the biosynthetic pathway to these compounds from chlorophyll-*a* is likely to be paralleled by the reported chemical synthetic routes (Ma & Dolphin, 1996a).

7. Concluding remarks

It is possible, even likely, that the use of chlorophyll metabolites by a species for a discrete biological function may be highly individualized, depending, perhaps, not only on the species itself, but also on the environment and mechanisms needed for survival. However, the essential nature of the possible biological activity seems to be inherent in the nature of the macrocycle. The tetrapyrrolic macrocycle represents one of the most common and widespread molecular architectures which nature is able to manipulate into a diversity of specialized biological functions. For example, by modifying the same precursor, uroporphyrinogen III (Jordan, 1991; Rudiger & Schoch, 1988), nature has biosynthesized chlorophylls, hemes and vitamin B_{12}; tetrapyrrolic macrocycles which play central roles in many fundamental biological functions such as photosynthesis (Scheer, 1991), electron transfer reactions

(Gouterman, 1978), nitrogen assimilation (Siegel & Murphy, 1973), *trans*-methylation (Battersby, 1993; Scott, 1993) and methane generation (Krone, Laufer, Thauer, & Hogenkamp, 1989). In this context, the dietary source of chlorophylls would appear to provide a seemingly inexhaustible treasury for herbivorous feeders.

Metal chelation strengthens the antioxidative activity of tetrapyrroles (Endo, Usuki, & Kaneda, 1985a). For example, at 30°C, 2 mM of chlorophyll-*a* (**1**) was superior by a factor of ca. two to 2,6-di-*t*-butyl-4-methylphenol (BHT), the best known synthetic antioxidant, on a molar basis; but pheophytin-*a* (**2**), the magnesium-free derivative of chlorophyll-*a*, showed an almost identical antioxidative activity to BHT during the autooxidation of methyl linoleate in the dark (Endo, Usuki, & Kaneda, 1985b). Electron spin resonance data indicate the presence of a chlorin radical cation during the oxidation of chlorophyll in methyl linoleate solution (Endo et al., 1985a). Similar π-cation radicals also have been observed in tetrapyrrolic compounds such as tetraarylporphyrins (Borg, Fajer, Felton, & Dolphin, 1970), bacteriochlorophyll and bacteriopheophytin (McElroy, Mauzerall, & Feher, 1974) after electrolysis, chemical oxidation or photolysis, and it is easy to generate the π-cation radicals from porphinoid compounds (Ravikanth, Misra, Reddy, & Chandrashekar, 1994; Jayaraj et al., 1996; Khindaria & Aust, 1996; Scheidt, Brancato-Buentello, Song, Reddy, & Cheng, 1996; Brancato-Buentello, Kang, & Scheidt, 1997; Ghosh & Vangberg, 1997; Rice-Evans, Miller, & Paganga, 1997). Thus it is reasonable to assume that π-cation radicals of chlorophyll metabolites may be involved with their antioxidative activity, although their mechanisms of action need further investigation.

Our current knowledge of chlorophyll metabolites and the relationship of composition and biological function are highly fragmentary. The 'fate' of chlorophylls in the human body remains essentially unexplored. In contrast to the large amount of chlorophylls metabolized by herbivores and humans, a mere handful of chlorophyll metabolites has actually been isolated and characterized. The limiting factor in undertaking these studies often results from the difficulty in identifying the possible biological function of metabolites. Significantly, most new chlorophyll metabolites have been isolated after biological screening of crude extracts for desirable activity. However, the connection between dietary chlorophylls and chemical ecology is continually being established, and further efforts to obtain structural and particularly biological information on these metabolites would add significantly to our knowledge in these areas. We hope, by throwing the spotlight on this often neglected subject, that we have focused attention on the latent possibilities that await exploration.

Acknowledgements

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