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Review Article

Skin bioavailability of dietary vitamin E, carotenoids, polyphenols, vitamin C, zinc and selenium

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Dietary bioactive compounds (vitamin E, carotenoids, polyphenols, vitamin C, Se and Zn) have beneficial effects on skin health. The classical route of administration of active compounds is by topical application direct to the skin, and manufacturers have substantial experience of formulating ingredients in this field. However, the use of functional foods and oral supplements for improving skin condition is increasing. For oral consumption, some dietary components could have an indirect effect on the skin via, for example, secondary messengers. However, in the case of the dietary bioactive compounds considered here, we assume that they must pass down the gastrointestinal tract, cross the intestinal barrier, reach the blood circulation, and then be distributed to the different tissues of the body including the skin. The advantages of this route of administration are that the dietary bioactive compounds are metabolized and then presented to the entire tissue, potentially in an active form. Also, the blood continuously replenishes the skin with these bioactive compounds, which can then be distributed to all skin compartments (i.e. epidermis, dermis, subcutaneous fat and also to sebum). Where known, the distribution and mechanisms of transport of dietary bioactive compounds in skin are presented. Even for compounds that have been studied well in other organs, information on skin is relatively sparse. Gaps in knowledge are identified and suggestions made for future research.

Bioavailability: Skin: Vitamin E: Tocopherol: Vitamin C: Ascorbate: Carotenoid: Polyphenol: Zinc: Selenium

The skin is the largest organ in man, consisting of different layers of epidermis and dermis. Its primary physiological function is that of a barrier between the body and the external environment, protecting against mechanical damage, radiation, toxic compounds and micro-organisms. Skin plays a role in the regulation of body temperature and is involved in body water homeostasis.

Skin is constantly exposed to pro-oxidant environmental stresses from an array of sources, such as air pollutants, solar UV light, chemical oxidants, micro-organisms, cigarette smoke and ozone (Thiele *et al.* 1997; Cross *et al.* 1998). Reactive oxygen species have been implicated in the aetiology of several skin disorders including skin cancer and photoageing (Perchellet & Perchellet, 1989; Dalle & Pathak, 1992; Emerit, 1992; Guyton & Kensler, 1993). These reactive oxygen species are capable of oxidizing lipids, proteins or DNA leading to the formation of oxidized products such as lipid hydroperoxides, protein carbonyls or 8-hydroxyguanosine, respectively (Beehler *et al.* 1992; Hu & Tappel, 1992; Podda *et al.* 1998). Reactive oxygen species are generated constantly in skin, and are rapidly neutralized by non-enzymatic and enzymatic antioxidant substances, which prevent their harmful effects and maintain a pro-oxidant–antioxidant balance, resulting in cell and tissue stabilization. If the antioxidant defence is exhausted, cell damage can occur. Known non-enzymatic scavengers of free radicals in human skin are β-carotene, vitamin C and vitamin E, and enzymatic scavengers are Se-dependent gluthathione peroxidases, Cu/Zn-superoxide dismutase, Mn-superoxide dismutase and catalase (Steenvoorden & van Henegouwen, 1997; Thiele *et al.* 2000). In recent years, particular antioxidants have gained considerable attention as a means to neutralize reactive oxygen species (Mukhtar & Ahmad, 1999). Green tea polyphenols (Katiyar & Mukhtar, 1997), resveratrol (Jang *et al.* 1997), curcumin (Stoner & Mukhtar, 1995), ginger (Katiyar *et al.* 1996) and diallyl sulfide (Sadhana *et al.* 1988; Perchellet *et al.* 1990) afford protection against the development of skin cancer, both *in vitro* (in culture systems) as well as *in vivo* (in animal models). Additionally, diets rich in bioactive compounds such as vitamins C and E, β-carotene, lycopene, Zn and Se have also demonstrated a photoprotective effect against solar irradiation in human subjects (Gollnick *et al.* 1996; Fuchs, 1998; Fuchs & Kern, 1998; McKenzie, 2000; Stahl *et al.* 2000, 2001; Greul *et al.* 2002; Rostan *et al.* 2002; Stahl & Sies, 2002; Cesarini *et al.* 2003).

Abbreviations: DCT1, H^+-coupled divalent cation transporter; hZIP4, human zrt-,irt-like protein; hZTL1, human zinc T-like transporter; MMP, matrix metalloproteinase; OATP, organic anion transporting polypeptide.

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An increase in cellular antioxidants in skin is observed after the exogenous administration of antioxidant compounds. In the case of the skin, the classical route of antioxidant administration is topical application. However, this topical route of administration can be achieved efficiently only if the particular antioxidant is stable in the preparation as well as on skin, is able to penetrate the skin and is present in its active form (i.e. possible metabolites). In addition, penetration of antioxidants into the skin is influenced by environmental factors, such as temperature, hydration and the presence of other chemicals. Another means to deliver antioxidants to the skin is through oral administration via the diet and dietary supplements. In this case, antioxidants cross the intestinal barrier and reach the blood circulation from where they are distributed to different tissues; specifically for skin to subcutaneous adipose tissue, dermis, epidermis and sebum. The advantages of this oral administration are that antioxidants are metabolized and then presented to the entire skin potentially in their active forms. In addition, the blood continuously replenishes the skin with these antioxidants, which are distributed to all skin compartments in which they could exert a biological activity.

In order to be active in skin, dietary bioactive compounds must be able to cross the intestinal barrier and reach the blood circulation. This step could be a limiting factor of the efficacy of these dietary bioactive compounds in skin. The present paper reviews current knowledge on the journey of dietary bioactive compounds from the mouth to skin with a special focus on antioxidants such as vitamin C, vitamin E, carotenoids, polyphenols, Zn and Se.

For the purposes of the present review, we have considered dietary compounds that have some 'antioxidant' properties, either direct or indirect. Because this group includes antioxidant vitamins (C and E), phytochemicals (carotenoids and polyphenols) and minerals (Zn and Se), we have grouped these compounds under the term 'dietary bioactives'.

Definition of bioavailability

Bioavailability is defined here by the relative amount of a dietary bioactive consumed that crosses the intestinal barrier, reaches the blood circulation and is available for metabolic processes or storage in the body; in this context, the skin. Bioavailability comprises various steps summarized by the acronym LADME. L means liberation of the molecule from the dietary matrix (food or supplement); A means absorption, i.e. transfer of the molecule from the gut lumen into the blood circulation; D refers to distribution of the molecule from the blood circulation into all body tissues (in this case the skin); M takes account of metabolism, consisting of the further processing of the molecule in the body either in the gastrointestinal tract or in various tissues; and E refers to elimination from the body in urine, stools, sweat, tears or expired air.

A brief comment on mechanisms of absorption in the gut

Dietary bioactives such as vitamin C, vitamin E, carotenoids (α- and β-carotene, lycopene, lutein, zeaxanthin and β-cryptoxanthin, astaxanthin, canthaxanthin), polyphenols (hesperidin, quercetin, rutin, genistein, daidzein, procyanidins, catechins), Zn and Se belong to two main groups: lipid-soluble and water-soluble dietary bioactives (Table 1). The solubility of a dietary bioactive markedly affects its mechanisms of bioavailability, which are reported in the following paragraphs.

Lipid-soluble or lipophilic dietary bioactives, e.g. vitamin E and carotenoids, are absorbed by the same pathway. In the stomach, these dietary bioactives are released from the food matrix and transferred into oil droplets, which are transformed in the small intestine into mixed micelles. The micellar solubilization of these lipophilic dietary bioactives is mandatory for their absorption; if lipophilic nutrients escape this solubilization, they continue their journey in the gastrointestinal tract and are subjected to either microflora metabolism in the colon or elimination. The uptake of lipid-soluble dietary bioactives by enterocytes was long considered a passive mechanism (Hollander *et al.* 1975; Hollander & Ruble, 1978; Fig. 1), but there is increasing evidence for facilitated, protein-carrier-mediated transport involving lipid transporters (During *et al.* 2002, 2005; Reboul *et al.* 2004; Fig. 2). Once inside

Table 1. Characteristics of dietary bioactive compounds ('dietary bioactives')

Solubility	Octanol–water partition coefficient at pH 7, 37°C (Cooper *et al.* 1997)	Class	Dietary bioactive	Example of food source
Lipid-soluble dietary bioactives	17·62	Carotenoid	α- and β-Carotene	Carrots, green leaves
	17·64		Lycopene	Tomato
	14·82		Lutein	Green leaves
	14·95		Zeaxanthin	Green leaves, corn
	16·08		β-Cryptoxanthin	Apples, apricots
	13·27		Asthaxanthin	Salmon, trout
	14·1		Canthaxanthin	Salmon, trout, egg yolk
	12·2	Vitamin	Vitamin E	Vegetable oil
Water-soluble dietary bioactives	−3·98	Vitamin	Vitamin C	Citrus, orange
	2·44	Polyphenol	Hesperidin	Orange
	1·48		Quercetin	Onions
	−1·11		Rutin	Tea
	2·53		Genistein	Soya
	2·55		Daidzein	Soya
	2·26		Procycanidin	Cocoa
	2·6		(+)-Catechin	Tea
		Trace element	Se	Cereals, seafood
			Zn	Oysters, red meat

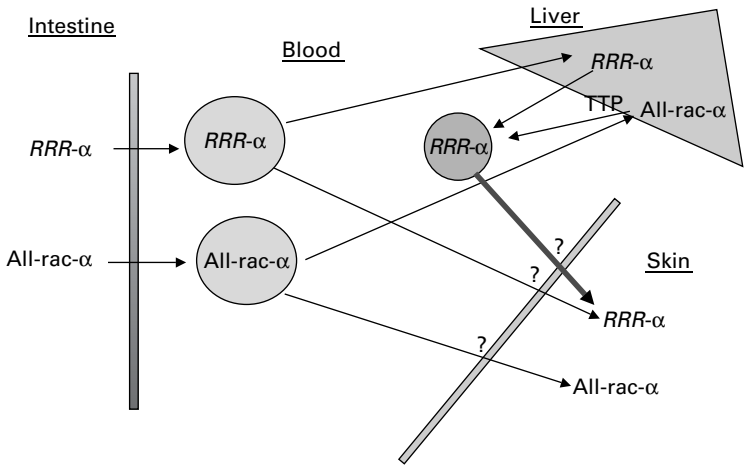

Fig. 1. A highly simplified representation of the mechanism of vitamin E absorption. *RRR*-α, *RRR*-α-tocopherol or natural vitamin E; all-rac-α, all-racemic-α-tocopherol or synthetic form of vitamin E containing eight different stereoisomers; TTP, tocopherol transfer protein.

the enterocyte lining the small intestine, these lipid-soluble dietary bioactives are packed into new oil-droplet structures called prechylomicrons, which are expulsed by exocytosis into the extracellular space, entering the lymphatic system and then reaching the general blood circulation.

In the particular case of water-soluble dietary bioactives, such as polyphenols and vitamin C, they remain in the bulk of the meal and arrive in the small intestine, since most polyphenols are stable in the stomach (Rios *et al.* 2002; Fig. 3). Many polyphenols are glycosylated in food, i.e. they are linked usually through a β-linkage to one or more glucose, arabinose, galactose or rhamnose residue(s). The glucose, and to a certain extent the arabinose and galactose residues, are hydrolysed by endogenous enzymes such as lactase present in the small intestine (Day *et al.* 2000; Nemeth *et al.* 2003) and the polyphenol molecule (aglycone) is then absorbed by the intestine. On the other hand, when polyphenols are bound to a rhamnose sugar such as in quercetin rhamnoglucoside (rutin), the brush border enzymes are not efficient at hydrolysing the polyphenol–sugar bond and therefore these molecules continue their journey in the gastrointestinal tract and reach the colon, where microflora possess the enzymes necessary to remove the rhamnose moiety from the polyphenol. At this stage, the polyphenol is either absorbed as such or metabolized further by bacteria into lower-molecular-weight metabolites, which are then absorbed by the colon. Some polyphenols, especially catechins and procyanidins, are not glycosylated, and so do not require deglycosylation before absorption. Within the enterocyte, most polyphenols are again conjugated but with glucuronide and sulfate moieties, although a proportion of some polyphenols, i.e. galloylated catechins and isoflavones such as genistein and daidzein, escapes this conjugation and is found partially in the unconjugated form in plasma (Manach *et al.* 2005). In consequence, blood contains a mixture of unconjugated and conjugated polyphenols resulting from intestinal metabolism and subsequent hepatic metabolism. Note that the exact nature of the polyphenol conjugates in blood is known only for a limited number of compounds (Kroon *et al.* 2004).

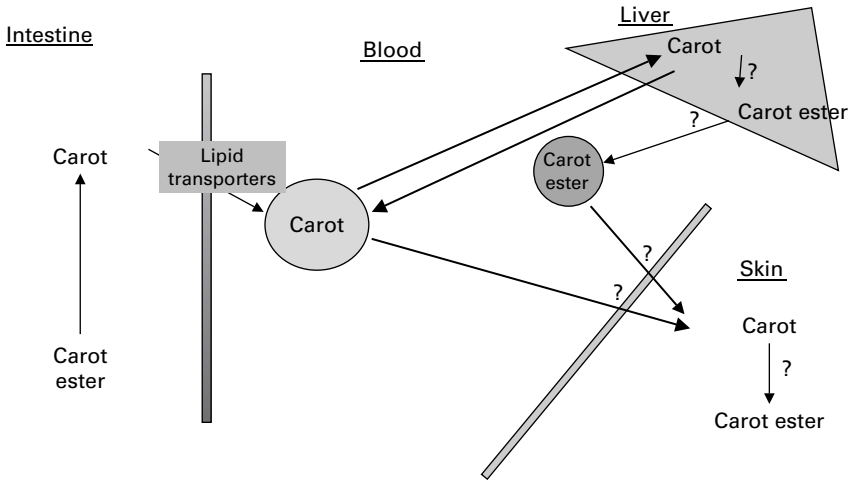

Fig. 2. A highly simplified representation of the mechanism of carotenoid absorption. Carot, carotenoids; Carot ester, carotenoid ester is carotenoid linked to a fatty acid moiety.

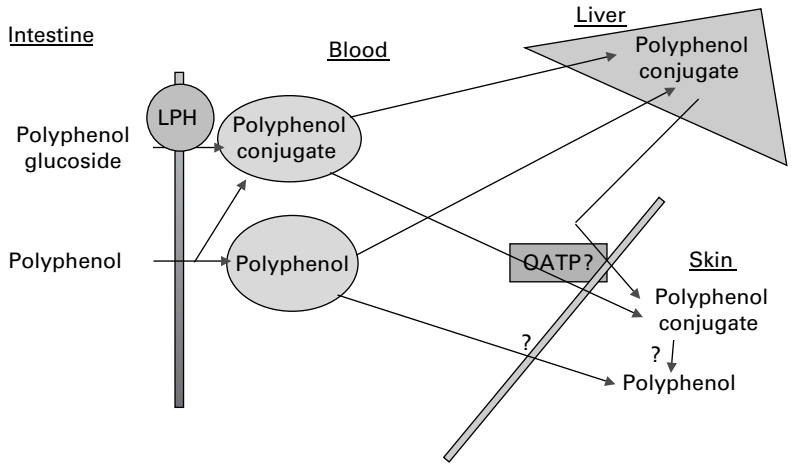

Fig. 3. A highly simplified representation of the mechanism of polyphenol absorption. LPH, lactase phloridzin hydrolase; OATP, organic anion transporting polypeptide (a transporter).

Vitamin C and dehydroascorbic acid are readily, rapidly and efficiently absorbed from the upper part of the small intestine into the blood circulation (Moser & Bendich, 1991) via Na^+-dependent active transport processes or by facilitated-diffusion glucose transporters (Liang *et al.* 2001; Fig. 4). Above 400 mg daily intake, plasma vitamin C remains constant due to higher renal and faecal excretion.

Trace elements occur in food in different forms, either inorganic forms such as oxyanions or organic forms such as linked to amino acids; these forms determine their pathway of absorption, i.e. passive or transporter-mediated. In the case of inorganic Se, selenate is absorbed by a sulfate transporter while selenite is absorbed by passive diffusion (Wolffram, 1995). Organic Se such as selenomethionine uses the same transporter as methionine (Fig. 5).

Zn is absorbed mainly by facilitated processes involving several transporters (Fig. 6). Ionized Zn uses different transporters such as hZIP4 (human zrt-,irt-like protein), which is the most predominant (Wang *et al.* 2002), while a cation diffusion facilitator (hZTL1, human zinc T-like transporter; Ford, 2004) and a H^+-coupled divalent cation transporter (DCT1) also play a role in Zn absorption. Complexed Zn, e.g. with amino acids, enters enterocytes via an H^+/peptide co-transporter (Evans, 1980; Hambidge *et al.* 1986; Tapiero & Tew, 2003). Moreover, a small proportion of Zn is absorbed by the paracellular route by either passive diffusion or solvent drag. Transporter-mediated or facilitated uptake is limited due to saturation of the transport systems or ion channels employed, and passive diffusion may be limited owing to numerous factors, e.g. physico-chemical properties (chemical form, degree of ionization and size). The concentration of trace elements in plasma is well controlled. Indeed, when intake is greater than the immediate tissue requirements, the excess is stored in some specific tissues (Fe in liver), excreted in urine (Se) or excreted back into the gastrointestinal lumen via gastrointestinal secretions or intestinal mucosal cell shedding (Zn).

Distribution and delivery to the skin

When dietary bioactives arrive in the blood circulation, they are ready to be distributed to all body tissues where they can exhibit a biological activity. Although certain dietary bioactives have been reported to exert a biological activity

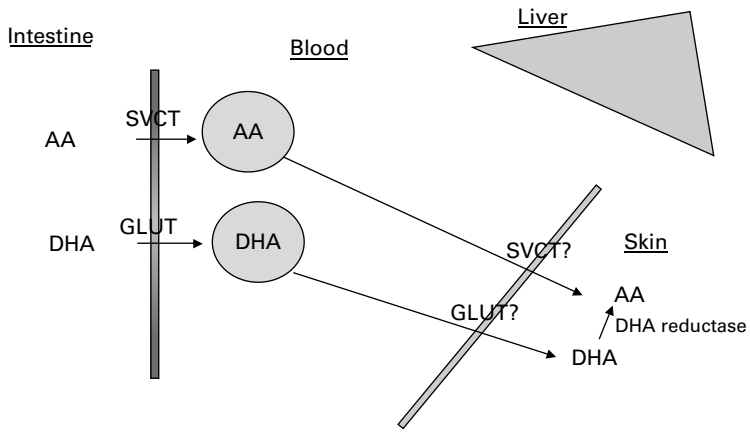

Fig. 4. A highly simplified representation of the mechanism of vitamin C absorption. AA, ascorbic acid; DHA, dehydroascorbic acid; SVCT, a Na^+-dependent transporter; GLUT, a glucose transporter.

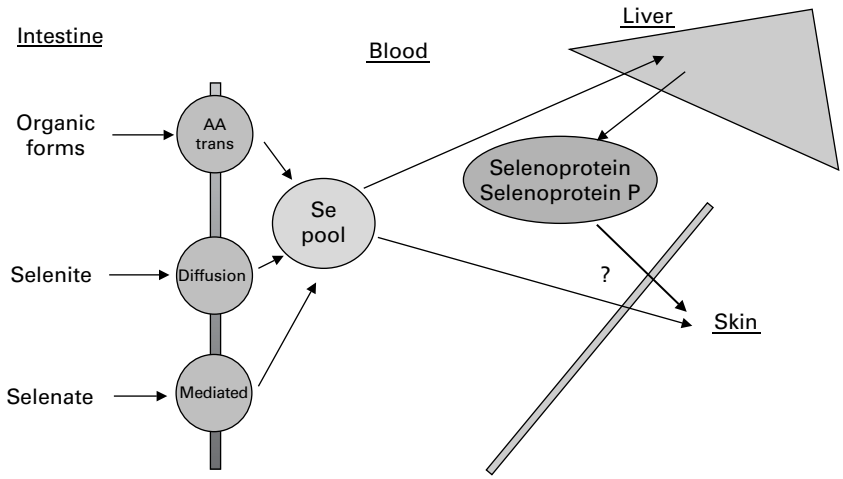

Fig. 5. A highly simplified representation of the mechanism of selenium absorption. AA trans, amino acid transporter.

in skin such as photoprotection, collagen synthesis and cancer prevention, information on their delivery mechanisms to skin is quite scarce.

Vitamin E

Vitamin E consists of a mixture of different molecules, i.e. α-, β-, γ- and δ-tocopherols and α-, β-, γ- and δ-tocotrienols. Due to the presence of three chiral atoms, these molecules exhibit different stereoisomers ranging from *RRR*, *RSR*, etc. to *SSS*. In response to supplementation, the concentration of vitamin E increases immediately in plasma while a rise in concentration is observed only after several days (7 d) in sebum (Vaule *et al.* 2004). The basis of this delay may be related to the process of sebum production, because it has been reported (Downing *et al.* 1981) to take approximately 8 d for newly synthesized lipids to be secreted in sebum. The delivery of vitamin E to skin seems to be very specific for certain isomeric forms (Fig. 1). Indeed, following supplementation, both the natural form (*RRR*-α-tocopherol) and the synthetic form (all-rac-α-tocopherol) appear in the blood circulation, whereas only *RRR*-α-tocopherol appears in sebum (Vaule *et al.* 2004). This indicates that a specific protein could selectively transport this form of the vitamin into the sebum. A similar specificity has already been described in the liver (Hosomi *et al.* 1997). γ-Tocopherol is absorbed into plasma but it is still uncertain whether γ-tocopherol exerts a biological activity in man since this form is mostly eliminated by the liver. However, γ-tocopherol is present in sebum and skin (Thiele *et al.* 1999; Vaule *et al.* 2004) and so it might exert an activity in human skin, although this needs further investigation. Skin vitamin E exhibits a gradient of concentration with a higher level in the dermis and a lower level in the stratum corneum (Shindo *et al.* 1994). In addition, there are regional variations of skin vitamin E; facial skin contains a several-fold higher level of vitamin E than unexposed skin sites such as skin from the upper arm (Thiele *et al.* 1998). This regional variability of vitamin E is supported by the fact that vitamin E is continuously delivered to sebum via the sebaceous glands (Thiele *et al.* 1999; Vaule *et al.* 2004). As a consequence, skin sites with high sebum production such as forehead skin exhibit higher vitamin E concentration (Lang *et al.* 1986).

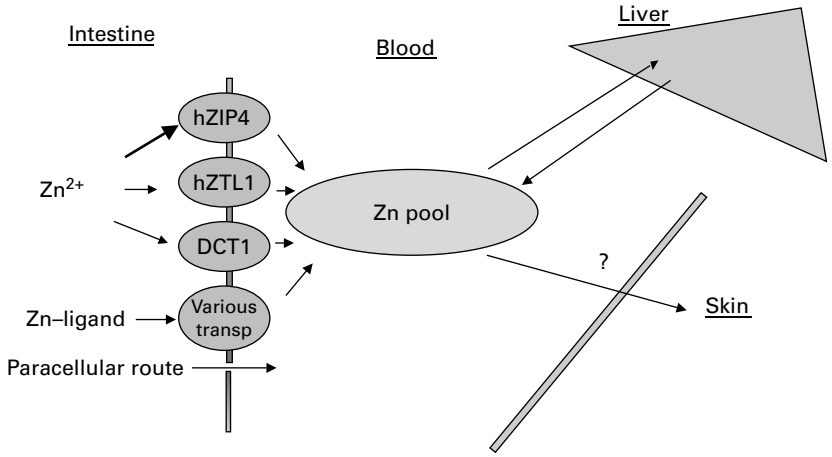

Fig. 6. A highly simplified representation of the mechanism of zinc absorption. hZIP4 (human zrt-,irt-like protein), hZTL1 (human zinc T-like transporter) and DCT1 (H^+-coupled divalent cation transporter) are transporters.

Carotenoids

Because carotenoids are lipophilic molecules, they are well placed to act as chain-breaking antioxidants in the skin protecting epidermal PUFA from peroxidation by oxygen radicals (Krinsky and Denecke, 1982). Carotenoid determination in skin is classically assessed by HPLC; however, this method is tedious and also quite invasive for the subject since it requires skin biopsy collection. Due to the polyene molecular structure of carotenoids, new non-invasive methods for the measurement of skin total carotenoid concentration have been developed such as reflection spectrometry (Jungmann *et al.* 1996) and Raman spectroscopy (Hata *et al.* 2000; Hammond and Wooten, 2005). Although skin total carotenoid levels measured with these two non-invasive techniques correlate with those obtained with HPLC, these methods provide the total carotenoid concentration rather than the concentration of individual carotenoids. In addition, these techniques measure carotenoids in the upper part of the skin, whereas punch biopsies provide information on the epidermal plus dermal content. It is difficult to quantify individual carotenoids because, for example, β-carotene exhibits a fourfold higher Raman scattering cross-section than lycopene with laser excitation at 488 nm (Hata *et al.* 2000). However, more recently, Raman spectrometry methodology has been adapted to quantify not only total carotenoids but also β-carotene and lycopene individually (Darvin *et al.* 2005) by taking into consideration the difference in absorbance between both substances and using an algorithm for the calculation of the absolute concentration of both carotenoids.

Carotenoid deposition in skin is not equal throughout the body (Hata *et al.* 2000; Stahl & Sies, 1996; Darvin *et al.* 2005) with the concentration decreasing in the following order: forehead > palm of hand > dorsal > inside arm = back of hand. Similarly to vitamin E, carotenoids might also be secreted in sebum and in consequence might explain the non-uniform level of skin carotenoids, but this needs to be further investigated. Carotenoids exhibit a concentration gradient with a higher amount in the dermis and lower levels in the stratum corneum. In addition, subcutaneous adipose tissue is rich in carotenoids, which could be a storage site of carotenoids for skin (Ribaya-Mercado *et al.* 1995). Skin β-carotene and lycopene are lower in smokers than in non-smokers and higher in vegetarians (Darvin *et al.* 2005).

Following supplementation, carotenoid concentration increases in skin (Stahl & Sies, 1996; Stahl *et al.* 1998, 2001; Postaire *et al.* 1997; Alaluf *et al.* 2002; Heinrich *et al.* 2003) but again to different extents at various skin sites: the increase is 2·4-fold in forehead, 0·7-fold in dorsal skin, 2·2-fold in the palm of the hand, 17-fold in the back of the hand and 1·7-fold for the inside of the arm. Most of the increase in skin carotenoid levels occurs within the first four weeks of supplementation but no plateau is reached during 12 weeks of supplementation. Cessation of supplementation induces a prompt drop of carotenoid level in all skin sites, decreasing by 56 % in forehead, 14 % in dorsal, 31 % for palm of the hand, 35 % for back of the hand and 47 % inside the arm (Stahl *et al.* 1998).

Besides the amount of total carotenoids delivered to skin, some attention needs to be given to how carotenoids reach the skin. For example, the carotenoid lycopene is a highly unsaturated molecule, containing thirteen double bonds among which eleven are conjugated. Of the theoretical 2^{11} geometrical isomer forms, only seventy-two are thermodynamically possible. All-*trans*-lycopene is the predominant lycopene isomer in nature, representing about 80–97 % in tomatoes and related products (Boileau *et al.* 2002). However, more than 50 % total lycopene is found in various *cis* forms in body fluids such as plasma (Krinsky *et al.* 1990) and breast milk, and in the prostate, testis and skin (Stahl & Sies, 1992; Clinton *et al.* 1996; Schierle *et al.* 1997; Wu *et al.* 2003). Investigators propose several explanations for this high proportion of *cis* isomers of lycopene in human, such as the preferential absorption of *cis*-lycopene isomers within the intestine (Stahl & Sies, 1992) or the isomerization of all-*trans*-lycopene in the stomach or intestine (Re *et al.* 2001); however, further investigation is required to identify the role of these *cis* isomers in human. Xanthophylls such as lutein and zeaxanthin are carotenoids containing hydroxyl groups and in consequence they could be either free or esterified with fatty acids. In fruits and vegetables, most xanthophylls are esterified. It is generally believed that these xanthophyll esters are hydrolysed during intestinal absorption. However, xanthophyll esters are present in skin, suggesting that either some xanthophyll esters have been absorbed as such or xanthophylls have been re-esterified in skin (Wingerath *et al.* 1998). Another aspect is the accumulation of specific carotenoids in specific tissues, such as lutein and zeaxanthin in the eye (Bone *et al.* 1988, 1997; Handelman *et al.* 1988) and lycopene and β-carotene in prostate (Clinton *et al.* 1996). This specific tissue accumulation suggests that the delivery of carotenoids to tissues involves facilitated processes. Indeed, evidence points to the implication of lipid transporters in carotenoid absorption by intestinal cells *in vitro* (Reboul *et al.* 2004; During *et al.* 2005). This facilitated transport of carotenoids could be also relevant in skin, but this needs to be investigated further (Fig. 2).

Polyphenols

Polyphenols are mostly present in plasma bound to albumin in conjugated forms, i.e. with glucuronide or sulfate, or methylated (Day *et al.* 2001; Kroon *et al.* 2004). Glucuronide conjugates of polyphenols would need to be transported actively into peripheral tissues because they are relatively hydrophilic and therefore diffuse through membranes only very slowly (Fig. 3). In certain tissues, conjugated polyphenols are hydrolysed by cellular β-glucuronidase activity, found both in the lysosomal fraction and in the lumen of the endoplasmic reticulum; in liver cells, this enzyme is active on quercetin glucuronides (O'Leary *et al.* 2003). Sulfatase activity is also present (Pasqualini & Nguyen, 1991) and acts on steroids and other sulfates inside the cell, thereby producing intracellular aglycone forms of polyphenols. The entry of polyphenol conjugates into hepatic cells is at least in part due to the organic anion transporting polypeptide (OATP) transporter class (O'Leary *et al.* 2003), and keratinocytes express some OATP transporters (Schiffer *et al.* 2003). While polyphenols are associated with a beneficial effect on skin (Kamimura & Takahashi, 2002; Ni *et al.* 2002; Singh & Agarwal, 2002; Mittal *et al.* 2003; Wie *et al.* 2003; Kenny *et al.* 2004; Widyarini *et al.* 2005), the exact mechanism of action is still

unknown, i.e. whether this action takes place directly via an increase of skin polyphenol content or indirectly through a systemic effect on the vascular system. Indeed, *in vitro*, the aglycone form of hesperidin is efficiently taken up by skin fibroblasts but does not protect them against UVA-induced damage, while hesperetin-7-glucuronide could not be detected in skin fibroblasts as an aglycone or a conjugated form, but is protective against UVA radiation (Proteggente *et al.* 2003). Silibinin, a polyphenol from milk thistle, appeared in mouse skin rapidly after absorption, but 90 % was metabolized or excreted within 4 h. The maximum amount of conjugated silibinin in skin was similar to that found in lung, liver and prostate, although the amount of the free form was lower: free silibinin, 1·4 μg/g (*v.* 8·8 μg/g in liver, 4·3 μg/g in lung, 2·5 μg/g in prostate and 5·8 μg/g in pancreas), and conjugated silibinin, 4·3 μg/g (*v.* 5·7 μg/g in liver, 2·8 μg/g in lung, 6·1 μg/g in prostate and 10·6 μg/g in pancreas) from a dose of 50 mg/kg. The liver exhibited the fastest elimination half-life, but the other organs were similar (half-life of about 100 min). There was also an increase in skin of the phase II enzymes, quinone reductase and glutathione *S*-transferase, which required 15 d administration to be maximal (Zhao and Agarwal, 1999). (−)-Epigallocatechin gallate, a polyphenol present in green tea, has been administered to the mouse. After consumption of ^{3}H-labelled compound, there was some radioactivity in skin (equivalent to 0·11 μg per 100 mg skin for a 1 mg dose). However, this is likely to be metabolites or breakdown products, protein-bound forms or even exchange with body pools of water, since the plasma kinetics using ^{3}H measurement did not match the pharmacokinetics using HPLC (Suganuma *et al.* 1998).

Vitamin C

Vitamin C is an effective antioxidant and an essential cofactor in numerous enzymatic reactions. It comprises two major forms: L-ascorbic acid, the reduced form, and L-dehydroascorbic acid, the oxidized form. Man and other primates have lost the ability to synthesize vitamin C as a result of a mutation in the gene encoding for L-gulono-γ-lactone oxidase, an enzyme required for vitamin C biosynthesis. In man, plasma ascorbic acid concentrations are maintained between 10 and 160 μM (1–15 μg/ml) and any excess of the vitamin is excreted by the kidney (Fuchs and Podda, 1997). Analysis of tissue ascorbate levels in human subjects revealed highest amounts in adrenal glands (550 mg/kg), brain (140 mg/kg) and liver (125 mg/kg), followed by lungs (70 mg/kg), kidneys (55 mg/kg), heart (55 mg/kg), skeletal muscle (35 mg/kg) and skin (30 mg/kg), and low levels in adipose tissue (10 mg/kg) and blood (9 mg/kg; Brown & Jones, 1996; Fuchs and Podda, 1997). Considering the different size and weight of the organs it is evident that ascorbic acid is concentrated in specific tissues, with the highest concentrations in adrenal glands, brain and liver, and the highest total amount present in skeletal muscle. In most of these tissues high ascorbate levels are probably important for maintaining structural integrity through collagen fibres, as well as for more specific functions, e.g. hormone synthesis, immune response and antioxidant protection. This concentration difference between different tissues clearly indicates that ascorbic acid uptake and distribution into tissues is mediated by an active transport mechanism. Indeed, two different ascorbic acid transporters, SVCT1 and SVCT2, have been identified by screening a rat kidney cDNA library (Tsukaguchi *et al.* 1999). SVCT1 is largely confined to epithelial surfaces involved in bulk transport, such as those of the intestine or kidney. In contrast, SVCT2 appears to account for tissue-specific uptake of vitamin C and is widely expressed, occurring in neurons, the endocrine system and other tissues. Recently, SVCT2-null mice have been generated. Surprisingly, the knockout is lethal perinatally, owing to respiratory failure and intraparenchymal brain haemorrhage in the animals. Most likely the observed haemorrhages are not a result of scurvy because the knockout mice showed no haemorrhages in other tissues and their skin had normal 4-hydroxyproline levels despite low ascorbate concentration. However, uptake of vitamin C by fibroblasts cultured from these mice was virtually abolished (Sotiriou *et al.* 2002). Interestingly, the organs with the most severe phenotypes were those that possessed the highest ascorbate concentration in man. In skin, *in vitro* studies in HaCaT keratinocytes demonstrated the presence and functional activity of both transporters, as well as an efficient ascorbate recycling system (Savini *et al.* 1999, 2000, 2002; Liang *et al.* 2001; Fig. 4). The latter might be an explanation for the mild skin phenotype of the SVCT2 knockout mice (Sotiriou *et al.* 2002). However, more work needs to be done to elucidate ascorbate transport in human skin.

Vitamin C distribution within the skin has also been determined in the murine model. Ascorbic acid concentration in the epidermis and dermis was 1·3 μmol/g (229 μg/g) and 1·0 μmol/g (176 μg/g), respectively; for dehydroascorbate, the concentration was 1·3 μmol/g in epidermis and 0·9 μmol/g in dermis (Shindo *et al.* 1994). Within the murine stratum corneum, the outermost layer of the epidermis, ascorbic acid exhibits a gradient of concentration with low levels in the outer layers and a steep increase in the deeper parts (Weber *et al.* 1999). Although skin was always thought to be the most sensitive organ during deficiency status (e.g. scurvy), recent results indicate that skin can cope with marginal amounts of vitamin C whereas other organs like brain and lungs suffer much more. However, under certain conditions the skin vitamin C pool can be depleted selectively, e.g. upon UV irradiation or in atopic dermatitic lesions (Shindo *et al.* 1994; Podda *et al.* 1998; Leveque *et al.* 2003), but whether that is due to a higher vitamin C turnover or a less efficient transport or recycling is not known at present. In contrast to ascorbate, the intestinal uptake of dehydroascorbate is mediated by facilitated-diffusion glucose transporters GLUT1, GLUT3 and GLUT4 (Liang *et al.* 2001). Under physiological conditions however, the reduced form of vitamin C will predominate (95 % in human plasma), and, thus, it is unlikely that GLUT-mediated dehydroascorbic acid uptake will be sufficient for the cellular demand of most cells. Furthermore, circulating levels of glucose are 1000-fold higher than dehydroascorbic acid levels (2–5 μM) and marked competition by glucose of dehydroascorbic acid influx is most likely (Liang *et al.* 2001). Furthermore, dehydroascorbic acid is nearly undetectable in most tissues (Rumsey and Levine, 1998). However, higher concentrations may occur transiently during oxidative stress.

Selenium

Most ingested Se, whether in organic or inorganic form, is converted by the liver into selenocysteine, which is used in the biosynthesis of selenoproteins including glutathione peroxidase and thioredoxin reductase. Evidence supports that selenoprotein P is a major transporter of Se from blood to other tissues, especially to brain and testis (Burk & Hill, 2005; Richardson, 2005). However, it is not clear how Se is delivered into cells. It would require specific membrane receptors to transport the selenoproteins; but evidence suggests the presence of such receptors has been found only in animal models (Wilson & Tappel, 1993; Burk & Hill, 1994). Se is present in skin cells (Fig. 5) as part of thioredoxin reductase and glutathione peroxidase, which exhibit major roles in the cellular defence against oxidative stress. Studies have showed that thioredoxin reductase is located on the cell membrane in keratinocytes and that this plays a vital role in protection from UV-induced free radical damage. Membrane-associated thioredoxin reductase correlates with different skin phototypes I–VI (Fitzpatrick classification), where darker skin has significantly higher enzyme activity than very fair skin. Higher levels of thioredoxin reductase have been found in black *v*. Caucasian skin (Schallreuter *et al.* 1987). Moreover, it is possible that the composition of selenoproteins in different skin cell types contributes to their well-known different susceptibility to UV-induced damage, and that genetic and racial differences in susceptibility to solar damage may reflect different genetically determined levels of expression of selenoproteins (McKenzie, 2000). Qualitative and quantitative differences have been shown in selenoprotein expression between keratinocytes, melanocytes and fibroblasts in culture (Rafferty *et al.* 1998). Keratinocytes have twice the specific activity of glutathione peroxidase of fibroblasts, and keratinocytes are more resistant to UV damage than fibroblasts (Leccia *et al.* 1998).

Total-body Se is 13 to 20 mg. Liver and kidney have the highest Se concentration (per weight of tissue), but these organs contain only a relatively small amount of total-body Se (4 % for kidney and 8 % for liver). About 40 to 50 % total-body Se is contained in skeletal muscles. It is important to note that some Se in muscles is incorporated unspecifically as selenomethionine instead of its methionine analogue. Brain, nervous and lung tissue have relatively low Se concentrations (Oster *et al.* 1988). Data related to Se concentration or distribution in skin are sparse and may depend on racial differences. One study showed that the epidermal:dermal ratio of Se is much lower than for Zn, Cu or Mn and varies between 0·8 and 1·5 in abdominal skin. As for other nutrients with antioxidant properties, this ratio depends on skin site and is much lower in plantar skin (Molokhia *et al.* 1979). Such a distribution is likely to be influenced by the type of environmental insult faced by skin on different parts of the body. There is some evidence of a hierarchy of tissue retention when Se deficiency occurs, with preferential accumulation of Se in brain, gonad, thyroid, pituitary and adrenal tissue over liver, erythrocytes, heart and muscle (Behne *et al.* 1988; Richardson, 2005). This could imply that a less-sensitive organ like skin could be depleted of its store in the case of inadequate Se intake or dietary restriction.

Zinc

In blood, 69 % Zn is transported with albumin, 30 % with α_2-macroglobulin and 1 % with the amino acids, cysteine and histidine (Hallman *et al.* 1971). The mechanism of delivery of Zn to skin is still unknown but might involve carrier proteins (Ackland *et al.* 1988; Guiraud *et al.* 1992; Fig. 6). The adult human body contains between 1·2 and 2·3 g Zn, of which 57 % is found in muscles (51 μg/g wet weight), 29 % in bone (100 μg/g wet weight) and 6 % in skin (32 μg/g wet weight; Jackson, 1989; King *et al.* 2000). The remaining Zn is found in all other tissues with 5 %, 1·5 %, 0·7 %, 0·5 %, 0·4 % and 0·1 % in liver (58 μg/g wet weight), brain (11 μg/g wet weight), kidneys (55 μg/g wet weight), blood (1 μg/g wet weight), heart (23 μg/g wet weight) and hair (150 μg/g wet weight), respectively. In skin, Zn exhibits a gradient of concentration, with five- to sixfold higher concentration in the epidermis (17 μg/g dry weight) than in the dermis (Molokhia & Portnoy, 1969). Zn plays an important role in the three skin functions, i.e. morphogenesis, repair and maintenance, and in protection and defence, since Zn is essential for catalytic, structural and/or regulatory functions of proteins and/or enzymes involved in these processes. The best described and with relevant activity in skin are the matrix metalloproteinases (MMP), superoxide dismutase, metallothionenein, alkaline phosphatase and those involved in regulation of gene expression, such as DNA and RNA polymerases. MMP, including collagenase (MMP-1), elastase (MMP-12) and gelatinase (MMP-2), are involved in the formation of extracellular matrix. Superoxide dismutase is important for its antioxidant properties, and metallothioneins store Zn and also have antioxidant properties. Alkaline phosphatase is involved in AMP metabolism, which plays a role in suppressing the inflammatory process. No tissue acts as a Zn store. Consequently when adaptation to low intake fails, deficiency can occur rapidly (Miller *et al.* 1994). During experimental Zn depletion in human volunteers, skin lesions were the most prevalent clinical sign (Prasad, 1982; Baer & King, 1984; Baer *et al.* 1985). Among other clinical signs and after biochemical modifications, moderate Zn deficiency is manifest by rough skin and delayed wound healing. In severe Zn deficiency such as acrodermatitis enteropathica, a gene mutation coding for hZIP4 transporter is associated with a defective absorption of Zn inducing dermatological manifestations such as bullous pustular dermatitis, erythema, areas of eczema and alopecia.

Conclusions

Different data support the fact that dietary bioactives such as vitamins, carotenoids, polyphenols and trace elements contribute to maintenance and improvement of skin integrity and physiology, as well as preventing deleterious effects induced by ageing and environmental stress. Beneficial effects have been demonstrated in various experimental systems including topical application of some of these ingredients. More recently, oral supplements containing various dietary bioactives have also been reported to be beneficial for skin. However, oral consumption does not guarantee obtaining a beneficial effect on human skin. Although some components of the diet could act by secondary messengers from the gut

or other organs to the skin, we assume that the dietary bioactives described here must cross the intestinal barrier and be metabolized and distributed to the skin in order to be effective. On the basis of present understanding of the key parameters involved in the absorption process, it is likely that the absorption of dietary bioactives in the gut, but also in skin, could be modulated by e.g. transfer proteins, the physical and chemical properties of the dietary bioactive, and competition and/or interaction with other dietary bioactives.

There are large gaps in knowledge in the area of skin bioavailability of dietary bioactives, despite some good evidence for beneficial effects of some of these components on skin in several *in vitro* and *in vivo* models. For example, the distribution and activity in skin of transporters for these compounds are almost completely unknown. The distribution between different compartments and body areas of skin is only known for some compounds, and turnover and export of dietary bioactives in skin are poorly studied.

The administration of dietary bioactives by the oral route offers several advantages over their topical application: intestinal absorption of bioactives, which are sometimes compromised in topical application owing to their low stability or low skin penetration; bioactives reach the entire skin of the body; and bioactives are distributed to all skin compartments, e.g. epidermis, dermis, hypodermis, blood vessels and sebum, allowing bioefficacy in all these compartments. The oral administration of these bioactives could also be complementary to the topical application.

The effects of ageing on skin health will always remain an important issue for the population, and educating them about what has or has not been established scientifically is an important role for health-care professionals. Additionally, further education on these ingredients, products and oral skin health supplements in general may ultimately drive future research that will distinguish truly efficacious nutrients from those with misleading claims.

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