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REVIEW

Influence of Polyphenols on the Physiological Processes in the Skin

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In the last decade antioxidants from a group of polyphenols have been proposed as one of the most effective functional ingredients of anti-ageing properties that counteract the effects of oxidative damage to the skin. It has been shown that the use of polyphenols affects skin protection and mitigates inflammatory conditions of the skin. Numerous studies have confirmed that polyphenols by neutralizing free radicals, antioxidant activity and by their ability to chelate ions of transition metals can effectively reduce the level of nonprotein inflammatory mediators. The biological activity of polyphenols in the skin is primarily determined by their physicochemical properties and the ability to overcome the epidermal barrier as they try to reach appropriate receptors. This study reviews literature on the effects of polyphenols relating to the physiological processes in the skin and role of the major plant polyphenols in cosmetology and dermatology. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: polyphenols; dermal bioavailability; antioxidant capacity; antiinflammatory activity.

INTRODUCTION

Polyphenols are a group of chemical compounds diverse in terms of structure and properties, which are classified as secondary metabolites. They can be found in different parts of plants, including flowers, fruits, seeds, leaves, roots and bark layers, and their main biological activity is to protect against biological stressors, harmful effects of ultraviolet (UV) radiation, viruses, bacteria and fungi and also to assist in the process of adaptation to changing environmental conditions, cellular signal transduction or gene expression (Harborne, 1986; Dewick, 1995; Korkina *et al*., 2007; Ververidis *et al*., 2007).

In the literature, different classifications of polyphenolic compounds can be found. Originally, simple phenols, phenolic acids, flavonoids, quinones, coumarins, lignans, stilbenes and tannins were included in this group (Harborne, 1989). Nowadays, according to different classifications, phenolic acids, flavonoids, stilbenes, lignans, coumarins and tannins are classified to the group of polyphenols (Quideau *et al*., 2011). However, in cosmetology and dermatology, the most important are flavonoids and phenolic acids (Nichols *et al*. 2010; McClain and Watson, 2013). The examples of major plant polyphenols applied in cosmetology and dermatology are shown in Table 1 and Fig. 1.

A common feature determining physicochemical properties of polyphenolic compounds is the presence of phenolic ring of hydrophobic character and one or more, hydrophilic in nature, hydroxyl groups. This specific design makes their molecules capable of interacting with other biomolecules, especially proteins, either through interactions such as van der Waals forces, hydrogen bonding interaction or dipole–dipole (Dangles and Dufour, 2008). Needless to say, that the structure and physicochemical properties of polyphenols underlie their biological activity in the skin. This study reviews literature on the effects of plant polyphenols relating to the physiological processes in the skin: antioxidant and antiinflammatory properties and antiageing activity. Many studies present the antioxidant activity of plant extracts rich in polyphenols, but until now, there have been no reviews presenting the complex information about dermatological and cosmetic properties of individual polyphenols starting from the characteristics and physicochemical properties of polyphenols and dermal bioavailability and ending with the impact of polyphenols on the physiological processes in the skin. For this reason, this study provides an overview of the current knowledge on the dermatological and cosmetic properties of plant extracts rich in polyphenols and individual polyphenols activity in the skin.

Characteristics and physicochemical properties of polyphenols

Polyphenols may occur both in the form of simple molecules such as phenolic acids and highly polymerized compounds such as tannins. On the other hand, hydroxy groups of polyphenols may be methylated, sulfonated, acylated by aryl or aliphatic acids and glycosylated by sugars (glucose, galactose, rhamnose, xylose and arabinose) and sugar acids (galacturonic acid or glucuronic acid) (Jasiński *et al*., 2009). Most plant polyphenol glycosides occur in the form of beta-O-glucoside or 1-6, 1-2 or 1-4 alpha O-glycosidic linkages bonded to the aromatic ring through the hydroxyl group (Fig. 2). Less frequently, these compounds appear in the form of C-glycoside connected by a

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Table 1. The examples of major plant polyphenols applied in cosmetology and dermatology

Plant	Active ingredients
Arnica montana	apigenin, luteolin, kaempferol, quercetin and its glycosides: 7-O-β and 3-O-β-glucoside, acetyl-β-glycosides and β-glucuronides, coumarins: umbelliferone, scopoletin
Calendula officinalis (pot marigold)	isorhamnetin, quercetin and their glycosides: 7-O-β and 3-O-β glycoside, rutin
Camellia sinensis (green tea)	catechin (-)-epicatechin, (-)-epigallocatechin-3-gallate, (-)-epicatechin gallate, (-)-gallocatechin, (-)-epigallocatechin, theaflavin
Curcuma longa (turmeric)	curcuminoids: curcumin (diferuloylmethane), desmethoxycurcumin, bidesmethoxycurcumin and tetrahydroxycumarin,
Glycyrrhiza glabra (liquorice or licorice)	liquiritin, isoliquiritin, liquiritigenin, isoliquiritigenin and coumarins: glycyrin, umbelliferone, ligcoumarin, herniarin
Glycine soja (Glycine max)	daizein, genistein, genistin, 4,7-dimetoxygenisteine, biochanin A
Linum usitatissimum (flaxseed)	Lignans: secoisolariciresinol diglucoside (SDG), matairesinol, pinoresinol, lariciresinol, isolariciresinol and secoisolariciresinol
Matricaria chamomilla (common chamomile)	apigenin, luteolin and their glycosides: 7-O-β and 3-O-β glucoside
Punica granatum	delphinidin, cyanidin, pelargonidin, punicalin, pedunlulagin, punicalagin, ellagic acid and gallic acid and their glycosides and esters
Salvia officinalis	apigenin, luteolin and their glycosides: 7-O-β and 3-O-β glucoside
Scutellaria baicalensis	baicalein, baicalin, wogonin, scutellarein
Silybum marianum	silymarin (flavonolignans complex) consisting of: silybin (silibinin or silibin) and their isomers: silybin A, silybin B, isosilibinin A and isosilibinin B; isosilybin, silychristin, silidianin
Vitis vinifera	quercetin, kaempferol, and their glycosides: 7-O-β- and 3-O-β-glycoside, rutin, peonidin, cyanidin, delphinidin, resveratrol

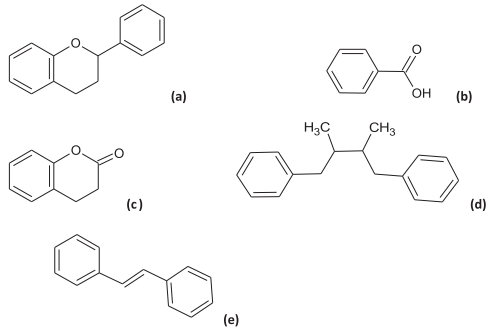

Figure 1. The base structures of major plant polyphenols (a) flavonoid; (b) phenolic acid, (c) coumarin, (d) lignan, (e) stilben.

glycosidic bond with a carbon atom at the phenyl ring (Bravo, 1998). Polyphenol glycoside bonds are characterized by better solubility in water and thus higher hydrophilicity as compared to aglycone forms. However, due to their high molecular weight and a lower lipophilicity, dermal bioavailability of polyphenol glycosides is lower compared to aglycone forms of these compounds (Fang *et al.*, 2006; Quideau *et al.*, 2011). The detailed data about the dermal bioavailability of polyphenol glycosides and aglycones are presented in the next section of this article.

Owing to low value of oxidation-reduction potential (ORP) ($E^{\circ} = 0.21$–0.75 V at $pH = 7$) and the half-life potential, polyphenols are characterized by a high chemical reactivity, which determines their antioxidant activity (Rice-Evans *et al.*, 1997; Korkina *et al.*, 2008). It has been also proven that polyphenol glycosides are characterized by lower antioxidant activity compared to their aglycone forms. *In vitro* studies have demonstrated that blocking a hydroxyl group in the polyphenol molecule with sugar residue has an influence on reducing antiradical properties of these compounds. Furthermore, glycosylation by disaccharide or trisaccharide residues significantly affects the deterioration of these properties when compared to glycosylation by monosaccharide residue. This is primarily related to large spatial dimensions of sugar residues. Present in plant extracts, polyphenol glycosides have a reduced cosmetic usability due to their low permeability of the epidermal barrier, thereby decreased penetration of the skin (De Groot and Rauen, 1998; Oborska and Arct, 2010). For this reason, it is preferable to use in cosmetology plant extracts rich in polyphenols of aglycone forms. Their extraction is possible through the use of chemical or enzymatic hydrolysis.

Another chemical characteristic of polyphenols affecting their antiradical activity is the ability to chelate ions metals such as Fe^{2+}, Fe^{3+}, Cu^{2+}, Zn^{2+} and Mn^{2+}. In cosmetology,

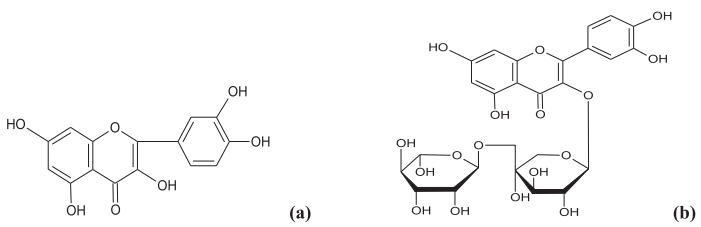

Figure 2. The aglicone (a) and glycoside (b) forms of polyphenols. Examples: (a) quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one) and (b) rutin (α-L-rhamnopyranosyl-(1 → 6)-β-D-glucopyranose).

the ability to chelate ions of multivalent metals is relevant in the context of limiting the activity of the enzymes, containing in their reaction centre metal ions or requiring metal cations cofactors (Kwak *et al*., 2005; Arct and Pytkowska, 2008). As demonstrated, polyphenols may affect, *inter alia*, lipoxygenase, cyclooxygenase, hyaluronidase, collagenase, elastase and tyrosinase and thus can contribute to the reduction of modifications in the skin under the influence of enzymes involved in connective tissue remodelling. Furthermore, the ability to chelate metal ions by polyphenolic compounds is beneficial for the inhibition of inflammatory processes and functioning of capillary vessels (Thring *et al*., 2009).

Other chemical properties of the polyphenol include the ability to absorb ultraviolet radiation, conditional on the presence of the conjugated double bonds. It has been shown that these compounds may absorb UV radiation in the range of 240–285 nm and 300–550 nm, which is associated with the presence of the electron-withdrawing or electron-donating substituents attached to the phenol ring, as well as intramolecular and intermolecular hydrogen bonds and steric effects. Polyphenol molecules can act as an exogenous chromophore (photosensitizers). After the absorption of quantum energy, they become excited and emit excess energy in the form of infrared radiation. However, due to the relatively low values of absorbance, polyphenols in concentrations found in cosmetics cannot replace conventionally used synthetic UVA and UVB filters. Nevertheless, they can be used as protective excipients (Arct and Pytkowska, 2008; Korkina *et al*., 2008). *In vitro* studies have demonstrated that plant extracts rich in polyphenols, particularly epigallocatechin-3-gallate from green tea, proanthocyanidine from grape seed, silymarin from milk thistle, soy isoflavones, curcumin, resveratrol and polyphenols present in the extract of pomegranate can significantly reduce erythema and skin burns caused by exposure to UVB radiation (Wright *et al*., 2006; Rhein and Fluhr, 2010; McClain and Watson, 2013; Mucha *et al*., 2013).

Transport through the skin and metabolism of polyphenols

The skin as the largest organ of the human body constitutes a barrier that on the one hand plays a key role in protecting the body against harmful external factors and xenobiotics, on the other hand limits penetration of active ingredients for cosmetic and dermatological purposes. The problem of bioavailability of externally applied active substances in cosmetology and dermatology is complex and determined by many factors (for example size and spatial structure of the molecule, polarity or lipophilicity) (Behl *et al*., 1993). Transport of active substances through the *stratum corneum* consists of the following steps: the vehicle penetration by a substance to the *stratum corneum*, diffusion of active ingredient in the *stratum corneum* and finally penetration of the *stratum corneum* into the living layers of the epidermis. The dynamics of this process depends both on biological factors (age, skin condition, cardiovascular functions and metabolism) and also physicochemical ones, such as a partition coefficient between the *stratum corneum* and the vehicle and related to it lipophilicity, as well as size, spatial structure of the molecule, polarity and load (Naik *et al*., 2000; Arct *et al*., 2001). As this process is complex, it is also relevant to differentiate the concentration of the tested substance in the base applied to the skin and the one in the *stratum corneum* or the presence of other substances in the vehicle (Arct *et al*., 2001; Subedi *et al*., 2010). It has been assumed that exogenous molecules of high molecular weight, greater than 3000 Da (or as some sources claim > 500 Da), and low lipophilicity have a limited ability to overcome the skin barrier (Bos and Meinardi, 2000; Abdelouahab and Heard, 2008). In the case of polyphenols, this problem is even more complex because these compounds depending on the form, free aglycone or glycoside, respectively, are characterized by moderate lipophilicity or hydrophilicity. In addition, polyphenols in accordance with the type have a variable size and spatial structure of the molecule. *In vitro* studies (Arct *et al*., 2002) with Frantz and Flynn chambers and model lipid membranes of *stratum corneum* have shown that individual polyphenols exhibit differences in penetration capacity, which substantially depend on the composition of the formulation in which these compounds are present. It has been proven that the penetration rate of flavonoids (rutin, quercetin and catechin) is affected by moisturizing substances such as glycerol, glycols, polyglycols, ethoxylated methylglucoside and urea and also by a cosmetic formulation (hydrogel, emulsion and micellar system) or content of the mixture in which active ingredients occur. This effect is also dependent on the type of flavonoid and whether it occurs in free form or the glycosidic one (Kanikkannan *et al*., 2000; Arct *et al*., 2002; Kogan and Garti, 2006). It is difficult to demonstrate obvious correlations by analysing published literature on penetration of flavonoids, and available research findings are often divergent, depending on whether these studies have been carried out *in vivo* (dermal absorption through human skin models) or *in vitro* (with Frantz and Flynn chambers and model lipid membranes of *stratum corneum*). On one hand, *in vitro* has shown that naringenin and hesperidin penetrate through the epidermis while quercetin penetrates poorly (Saija *et al*., 1998). On the other hand, other authors have proven that of these compounds, quercetin, in particular (Bonina *et al*., 1996), has the best possible penetration of the *stratum corneum*, and naringenin and hesperidin penetrate the skin much faster in the presence of D-limonene and lecithin (Saija *et al*., 1998). In other studies (Fang *et al*., 2006; Diniz *et al*., 2007), limited penetration capacity has been observed for rutin, (+)-catechin, (-)-epicatechin, quercetin and verbascoside. Their presence has been confirmed only in the superficial layers of the *stratum corneum*. Other *in vitro* assays have demonstrated that caffeic and chlorogenic acid penetrate the *stratum corneum* faster than oraposide, a natural glycosidic phenylpropanoid (Marti-Mestres *et al*., 2007). In turn, *in vivo* studies have discovered that aglycones of flavonoids exhibit significantly better penetration capabilities in comparison to their glycoside form. It has been shown that flavonoid apigenin penetrates better than its apigenin 7-O-β-glucoside (Merfort *et al*., 1994). However, in the case of hydroxyethylorutoside, penetration into the *stratum corneum* has been observed despite glycoside form, and in the case of certain derivatives (trihydroksyethylrutoside and dihydroxyethylrutioside), reaching the dermis with no hydrolysis of these compounds detected in the epidermis and dermis (Jung and Steche, 1972).

Despite numerous discrepancies in the test results of polyphenols' permeation, several authors suggest that permeability of these compounds increase when liposomes and assisted transport techniques, electroporation and iontophoresis, are used. The increase in dermal bioavailability of polyphenolic compounds is also affected by the presence of the permeation promoters (glycerin and propylene glycol), which may affect the membrane by improving its permeability (Arct *et al*., 2002; Fang *et al*., 2006; Subedi *et al*., 2010). After overcoming the epidermal barrier, polyphenolic compounds may be subject to nonenzymatic transformation or interaction with Phase I and II enzymes. In the case of nonenzymatic transformation of polyphenolic compounds in the skin, this activity is related, for example, to the interaction with reactive forms of nitrogen (nitric oxide and peroxynitrite) (Afanas'ev, 2007; Korkina *et al*., 2012).

Phase I enzymes of polyphenol metabolism, such as cytochrome P450 (CYP) enzymes, catalyse reactions of hydrolysis, reduction and oxidation with ensuing increased hydrophilicity of xenobiotics by their biotransformation in the process of attachment of corresponding functional groups: hydroxyl (-OH), carboxyl (-COOH), thiol (-SH) or amino (-NH_2) (Gonzalez *et al*., 2006). In the skin, mainly cytochrome P450 (CYP) participates in the catalysis of this phase of xenobiotic metabolism. CYP isoforms are active CYP1A1 (basal layer), CYP1B1 (spinosum and stratum granulosum), CYP2B6 / 7 (keratinocytes, dendritic cells), CYP2E1 (keratinocytes, dendritic cells), CYP3A4 / 7 (keratinocytes, dendritic cells), and their activity is conditional on the presence of molecular oxygen and NADH (Katiyar *et al*., 2000; Villard *et al*., 2002; Korkina *et al*., 2008). In the second phase of xenobiotics biotransformation transferases, UDP-glucuronosyltransferases (UGT), glutathione-S-transferase (GST) and catechol-O-methyltransferase (COMT) are mainly involved. Phase II enzymes catalyse the reactions of acetylation, methylation and coupling of amino acids by glucuronic, acetic or sulfuric acid that give rise to the transformation of hydrophilic derivatives of the compounds mostly biologically inactive and safe for the body (Gonzalez *et al*., 2006). Ensuing metabolites may act on skin cells, both in an antiinflammatory, antioxidant and antimicrobial way, and may also exhibit pro-oxidative, cytotoxic or phototoxic properties. The effect, however, depends mainly on the type of polyphenolic compound and its physicochemical properties and the type of transformation involved (Baron *et al.*, 2001; Ahmad and Mukhtar, 2004).These processes are described in detail in the works of Korkina *et al.* (2008), Gonzalez *et al.* (2006) and Oesch *et al.* (2007).

Antiinflammatory properties of polyphenols

The activity of such external factors as UV radiation, cigarette smoke and pollution may contribute to the formation of free radicals, reactive oxygen forms or nitrogen in the skin. All these formations are primarily associated with the induction of multiple biological responses associated with the activation of nuclear transcription factor kappa B (NF-kappaB) and AP-1 transcription factors, which regulate secretion of pro-inflammatory cytokines, tumour necrosis factor alpha (TNF-α), interleukin (IL-1, IL-6, IL-8), thereby inducing skin inflammation. One of the main functions of polyphenols in the skin is the ability to inhibit pro-inflammatory cytokines and enzymes activity, mainly iNOS (inducible nitric oxide synthase), NADPH oxidase (nicotinamide adenine dinucleotide phosphate-oxidase), COX-1 (cyclooxygenase-1), COX-2 (cyclooxygenase-2), 5-LOX (arachidonate 5-lipoxygenase), 12-LOX (12-lipoxygenase), 15-LOX (15-lipoxygenase), phospholipase A2 (Yoon and Baek, 2005; Pastore *et al.*, 2009; McClain and Watson, 2013; Nakamura *et al*., 2014).

In an inflammatory process, arachidonic acid is released from the cell membrane of phospholipids under the influence of phospholipase A2 (PLA2) (Fig. 3). This enzyme is activated by free radicals and lipid peroxidation products such as α, β-unsaturated hydroxyalkenale, saturated and unsaturated aldehydes, dialdehydes and ketones (malondialdehyde, acrolein and 4-hydroxy-2-nonenal) (Yoon and Baek, 2005; Burdan *et al*., 2006). Noteworthy is the fact that prostaglandin H synthase (PGHS), also known as the synthesis of prostaglandin cyclic peroxide, participates in the induction of an inflammatory response in the skin. This is a bifunctional enzyme exhibiting peroxidase and cyclooxygenase activity. In this reaction, cyclooxygenase converts arachidonic acid (AA) in prostanoids, prostaglandin G2 (PGG2), prostacyclin and thromboxane A2 (TXA2), whereas peroxidase component catalyses the reduction of prostaglandin G2 into prostaglandin H2 (PGH2). In the reaction, two isoforms are involved: COX-1, which is the constitutive isoform, and COX-2, the induced isoenzyme the expression of which is regulated by external factors such as ultraviolet rays, cytokines (TNF-α, IL-1), growth factors, liposaccharides and oncogenes (Herschman, 1996; Lee *et al*., 2003; Schwab *et al*., 2003). It has been proven that polyphenol compounds such as genistein, resveratrol, epigallocatechin gallate and ellagic acid can affect on the inhibition of an inflammatory response. *In vitro* evidence demonstrates that the COX-1 and COX-2 inhibition is observed in the presence of genistein, resveratrol and (-)-epigallocatechin-3-gallate, while quercetin through electron transfers can affect the increase of cyclooxygenase (Yoon and Baek, 2005; Rhein and Fluhr, 2010). The inhibitory activity of polyphenols on an inflammatory response may occur as early as at the beginning of the transformations and is associated with the neutralization of free radicals produced in the skin under the influence of exogenous factors, reactive oxygen species and nitrogen and through the inhibition of the lipids peroxidation process (Rhein and Fluhr, 2010). Polyphenols such as quercetin, kaempferol 3-O-galactoside and curcumin act additionally, under *in vitro* conditions, on the inhibition of PLA2 activity (Gil *et al*., 1994). The alternative to the transformations of arachidonic acid, catalysed by cyclooxygenase, is the lipoxygenase pathway in which three isoforms of the enzyme, 5-LOX, 12-LOX, 15-LOX, may participate (Fig. 3) in arachidonic acid transformations in the skin participate isoforms of 15-LOX-1,15-LOX-2 and 12R-LOX (Bickers and Athar, 2006; Gulliksson *et al*., 2007). In this process, the protective effect of polyphenols is primarily associated with the inhibition of the oxidative activity of LOX. This is chiefly achieved by polyphenols blocking the enzyme binding to the substrate through hydrogen bonding networks disturbance or through the chelation of iron ions present in the reactive centre of an enzyme (Arct and Pytkowska, 2008). This activity has

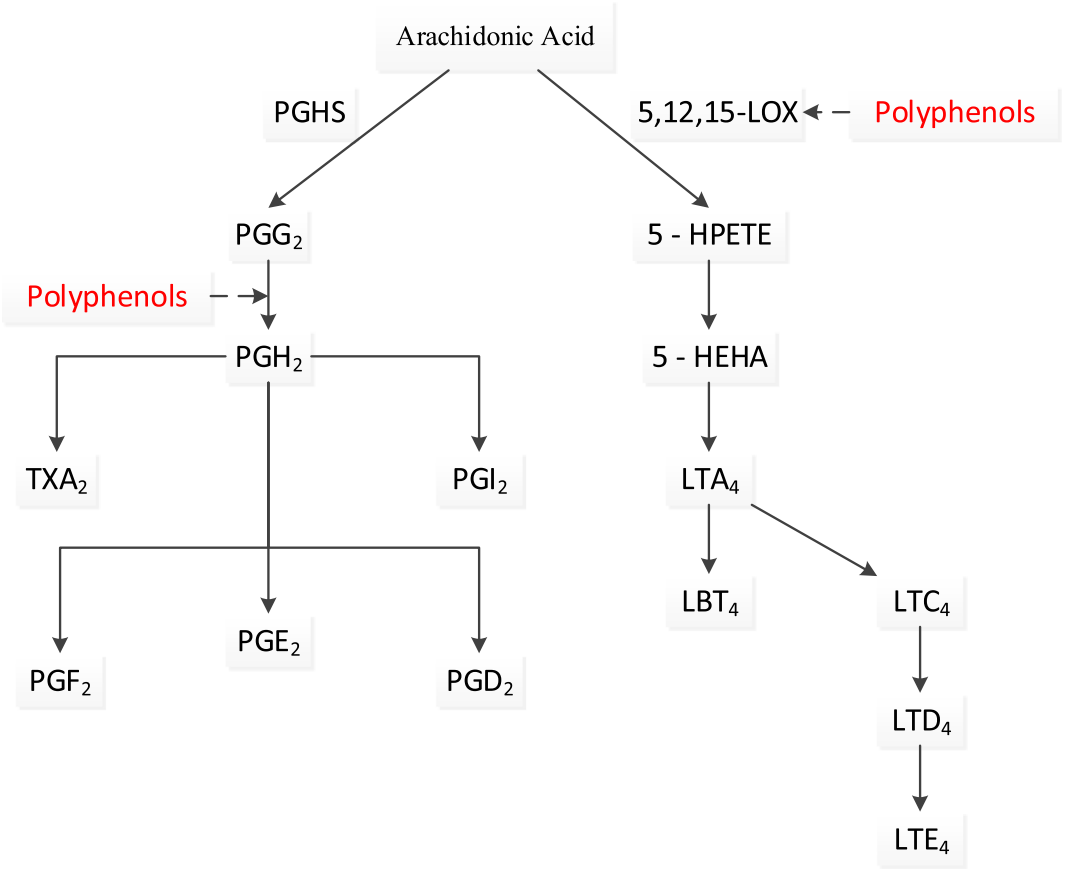

Figure 3. Inhibition of arachidonic acid conversion by polyphenols. On the figure, there are indicated places where polyphenols can act and inhibit the arachidonic acid conversion into proinflammatory prostaglandin, thromboxane and leukotriene. PGHS, prostaglandin H synthase; PGG_2, prostaglandin G_2; PGH_2, prostaglandin H_2; TXA_2, thromboxane A_2; PGI_2, prostacyclin I_2; PGE_2, prostaglandin E_2; PGF_2, prostaglandin F_2; PGD_2, prostaglandin D_2; 5, 12, 15-LOX, lipoxygenases; 5-HPETE, 5-hydroperoxyeicosatetraenoic acid; 5-HEHA, 5-hydroxyeicosatetraenoic acid; LTA_4, leukotriene A_4; LBT_4, leukotriene B_4; LTC_4, leukotriene C_4; LTD_4, leukotriene D_4; LTE_4, leukotriene E_4.

been demonstrated for apigenin, quercetin, kaempferol, myricetin and curcumin under *in vitro* conditions (Yoon and Baek, 2005; Rhein and Fluhr, 2010).

Another possible way of polyphenols interfering with an inflammatory response is their ability to inhibit the activation of transcription factors NF-kappaB and AP-1 that regulate the secretion of proinflammatory cytokines (TNF-α, IL-1, IL-6, IL-8) (Pastore *et al.*, 2009; Pastore *et al.*, 2012; McClain and Watson, 2013) (Fig. 4). Nuclear transcription factor kappa B (NF-kB) is a protein involved in intracellular signalling and pathogenesis of defence and inflammatory responses in the body. It is naturally found in the cytoplasm of most cells and in an inactive form creates a complex with p50 and p65 precursor proteins and inhibitory IkB proteins. Free radicals and reactive oxygen species (particularly H_2O_2), cytokines (IL-1β, IL-2, IL-17, IL-18, TNF-α), UV light, pathogenic bacteria and viruses, which activate the

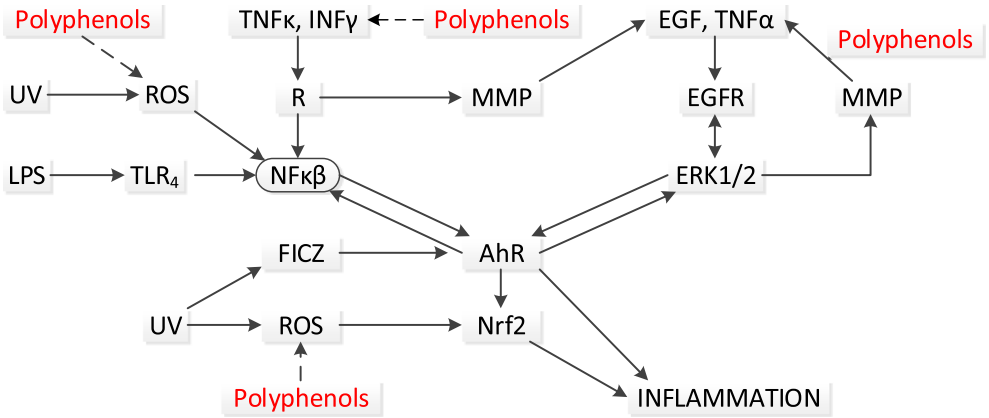

Figure 4. Inhibition of inflammation inducing factors in the skin by polyphenols. On the figure, there are indicated places where polyphenols can act and inhibit inflammation. UV, ultraviolet radiation; ROS, reactive oxygen species; NF-κB, nuclear transcription factor kappa B; Nrf2, nuclear erythroid 2-related factor; MAPK, mitogen activated protein kinases; MMP, matrix metalloproteinases; TGF-β1, transforming growth factor-β1; IFNγ, interferone γ; LPS, lipopolysaccharide; TLR_4, toll-like receptors; TNF-α, tumour necrosis factor; AP-1, activator protein 1; AhR, aryl hydrocarbon receptor; FICZ, 6-formylindolo-[3,2-b]-karbazole; EGFR, epidermal growth factor receptor; EGR, epidermal growth factor; ERK 1/2, extracellular signal-regulated kinase 1/2; p65, 65 kDa polypeptide; R, receptor.

kinases, MAPKs (mitogen-activated protein kinases), protein kinase Akt and the complex of IκB kinase, catalysing phosphorylation, ubiquitination and proteolysis of IkB proteins, are involved in the activation of NF-kappaB. The release of the transcription factor NF-kappaB and transfer to the nucleus, where it participates in the transcription of genes leading to the cell inflammatory response, is the result of this process. However, it may be inhibited by polyphenols activity, which exhibit not only the ability to inhibit IkB kinase, thereby blocking phosphorylation and degradation process of IκB, but also reduce the expression of pro-inflammatory cytokines TNF-α, IL-1, IL-6, IL-8. This function has been demonstrated *in vitro* and *in vivo* for silymarin, resveratrol, (-)-epigallocatechin gallate, quercetin and caffeic acid esters (Hou *et al*., 2004; Yoon and Baek, 2005). As shown, polyphenols, both in the form of aglycones (quercetin and resveratrol) but also glycosides (rutin and verbascoside), can successfully affect the protection of human keratinocytes by limiting, triggered by UVB radiation, the expression of NF-kappaB transcription factor (Pastore *et al*., 2008; Potapovich *et al*., 2011). Apart from the NF-κB transcription factor, there is also the AP-1, factor and both these factors are responsible for the expression of genes encoding proteins that regulate cell cycle, inflammatory responses, immunomodulatory effects and antiapoptotic cells (Portugal *et al*., 2007). The AP-1 transcription factor is a heterodimeric protein of structure consisting of two subunits of c-Jun and c-Fos. The modulation of AP-1 activity in keratinocytes is affected by free radicals, reactive oxygen species and UVB radiation. This leads to the activation of MAPKs, ERK (signal-regulated kinases) and JNK (c-Jun amino-terminal kinases), which regulate respectively the transcription of c-Fos gene and phosphorylation of c-Jun subunits, resulting in the AP-1 transcription factor activation (Bickers and Athar, 2006). It was proven that polyphenolic compounds may indirectly regulate the activity of AP-1 through free radicals inhibition or interaction with MAPKs. Effects on mitogen-activated protein kinases may vary depending on the type of polyphenolic compound and its redox potential. For (-)-epigallocatechin gallate and rutin MAPKs, activation was observed in keratinocytes, and thus the activation of AP-1, while in the case of verbascoside and quercetin, MAPKs inhibition was observed. In addition, these compounds may act on the inhibition of cytokine IL-8, IL-10, which *inter alia*, are responsible for the apoptosis of keratinocytes (Rhein and Fluhr, 2010). Therefore, polyphenols may indirectly influence the normal process of proliferation and differentiation of the epidermal basal layer cells (Balasubramanian and Eckert, 2007; Portugal *et al*., 2007).

Cosmetic and dermatological properties of polyphenols

Polyphenolic compounds belong to the most frequently used in modern cosmetology and dermatology active ingredients of cosmetics with antiradical and antiageing properties (Masaki, 2010; Anunciato and da Rocha Filho, 2012; McClain and Watson, 2013). Their popularity is mainly connected with antioxidant properties. It should be noted that in addition to this function, the compounds demonstrate in *in vitro* studies the ability to inhibit enzymes and protein bindings but can also impact microcirculation and, thus, may affect functions of the skin. Furthermore, polyphenol compounds due to their antioxidant and antiinflammatory properties may be the ingredient in a daily care of vascular, oily and atopic skin. Examples of major polyphenols applied in cosmetology and dermatology are shown in Table 1.

Antiageing properties of polyphenols. In addition to the already described possibilities of lipoxygenase and cyclooxygenase inhibition, polyphenol compounds may also affect the modulation of protease activity, especially matrix metalloproteinases. This property is associated with the ability of polyphenolic compounds to sequester polyvalent metal ions, which are cofactors or catalytic factors in the reactive centre of an enzyme. Matrix metalloproteinases are dependent on Zn^{2+} ion of enzymes involved in connective tissue remodelling. Phenolic compounds have been shown to play a significant role in their activity either by sequesting metal ions or the effect they have on the expression of endogenous protein tissue inhibitors of metalloproteinases (TIMP), especially TIMP 1 and 2. *In vitro*, these properties have been confirmed for (-)-epigallocatechin gallate, (-)-epicatechin gallate and theaflavin. Moreover, there has been observed for (-)-epigallocatechin gallate the effect of the inhibition of metalloproteinase activity through the inhibition of membrane-type matrix metalloproteinase (MT-MMP), which are necessary to activate pro MMP2 (Bickers and Athar, 2006; Masaki, 2010; OyetakinWhite *et al*., 2012).

Skin-whitening activity of polyphenols. Chelating ability of polyphenolic compounds may be also used in the modulation of tyrosinase activity. This enzyme belongs to the oxidoreductases with Cu^{2+} ion in the reactive centre catalysing oxidation of tyrosine to L-DOPA (L-3,4-dihydroxyphenylalanine) and then to the L-dopaquinone, which is part of the melanogenesis process. The ability of tyrosinase inhibition under *in vitro* conditions has been observed for cyanidin, quercetin and kaempferol, while glycosidic forms have showed no such capability. Additionally, polyphenols can also reduce the process of melanogenesis through the inhibition of tyrosinase activity in melanocytes or a reduction in melanocytes proliferation. *In vitro*, these effects have been demonstrated for hesperidin, naringenin, proanthocyanidins and ellagic acid. One of functions of antiageing products is to prevent the formation of senile lentigines (lentigo senilis) and solar lentigo (lentigo solaris). Hence, the possibility of influencing tyrosinase activity by polyphenolic compounds is of great importance and practical application in the field of antiageing preparations whose function is to prevent the formation of senile lentigines (*lentigo senilis*) and solar lentigo (*lentigo solaris*) (Kim *et al*., 2006; Xue *et al*., 2011).

Estrogen-like effects of polyphenols. The polyphenol isoflavones have a specific structure and properties that make them exhibit under *in vitro* conditions structural similarity to certain biologically active endogenous substances (adrenaline, noradrenaline, L-tyrosine, L-DOPA, thyroxine and estrogens), as well as to protein receptors. The isoflavones have ring B attached to ring C at position 2, and the hydroxyl groups are present at position 7 and 5 (Fig. 5). Therefore, such a structure of isoflavone molecule resembles the chemical structure of 17β-estradiol. These interactions with protein receptors take

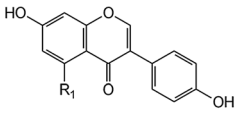

Figure 5. The structures of isoflavones. R_1, H in daizein; R_1, OH in genistein.

place at molecular level and are related to the van der Waals interactions and hydrogen bonds between proteins and polyphenols. Therefore, these compounds may affect the activity of cytochrome P450 enzymes, cyclooxygenase and lipoxygenase and bind to protein receptors peroxisome proliferator-activated receptor (PPAR) and estrogen receptor (ER), thereby influencing the inhibition of inflammatory responses or regular proliferative processes and differentiation of keratinocytes. The ability of binding to estrogen receptors, (both ERα and ERβ) is also of relevance in antiageing cosmetology. Activation of ER receptors is performed by attaching 17β-estradiol to the estrogen responsive receptors (ERR) or its interaction with protein transcription factors NF-κB or AP-1, which in consequence results in the transcription of genes responsive to estrogen. As demonstrated, ligands with at least two phenol rings with the hydroxyl group at position 4′, 7, 5 and none of the methoxy group in the 4-position in their structure show the affinity for the ER receptors. Specific predispositions, mainly due to the flat structure and the ability of electron delocalisation within three rings are displayed by isoflavones. Structural similarity to 17β-estradiol is a distinctive feature for certain of polyphenolic compounds from the group of flavonoids occurring in the form of aglycones, especially isoflavones (genistein, daizein, biochanin A and formononetin), lignans (enterolactone and enterodiol), flavonoids (kaempferol, quercetin and apigenin) and stilbenes (resveratrol) (Arct and Pytkowska, 2008; Dangles and Dufour, 2008; Korkina *et al*., 2008; Rhein and Fluhr, 2010). *In vitro* studies on these ligands have demonstrated that they have higher affinity to ERβ than to ERα, but their activity is much weaker compared to steroidal estrogens. Interaction of polyphenols with proteins is also associated with the ability to form hydrogen bonds between the hydroxyl or ketone groups of polyphenols and carbonyl, amide or hydroxyl groupings present in the protein chain. This feature is characteristic of a cosmetic use of tannins found in the extract of green tea, especially oligomeric proanthocyanidin. These compounds by forming hydrogen bonds with protein structures of the epidermis show astringent and improving skin tone proprieties (Arct *et al*., 2003; Kostelac *et al*., 2003).

Influence of polyphenols on microcirculation and blood vessels. Phenolic compounds can also affect the skin microcirculation, mainly through a protective effect on blood vessel walls, reduction of capillary permeability and by facilitation of blood free flow through the capillaries as a result of platelet aggregation inhibition. All these properties have a practical application in the prevention of telangiectasia and the protection of blood vessel walls. It is possible mainly owing to the ability of polyphenols to neutralize free radicals produced by the neutrophilic granulocytes during phagocytosis and also thanks to the protective ability of polyphenols in relation to vitamin C, which is essential for the synthesis of collagen building vascular walls. Furthermore, polyphenols affect blood vessels strengthening through the inhibition of the neurohormone of adrenaline oxidation to adrenochrome that affects the weakening of blood vessels by reducing the time of their contraction. Polyphenols activity is related to their ability to chelate iron and copper ions, which are catalysts in the process of adrenaline autoxidation. *In vitro*, green tea polyphenols are active ingredients acting on the inhibition of neurohormone oxidation, notably, epicatechin (Arct and Pytkowska, 2008). In addition, *in vitro* studies on catechin and quercetin have demonstrated that the modulation of cyclooxygenase activity can suppress telangiectasia formation by the ability of these polyphenols to prevent inflammatory conditions, particularly by inhibiting the secretion of thromboxanes, substances with proinflammatory and disrupting microcirculation qualities (Guerrero *et al*., 2005). Polyphenolic compounds, such as apigenin, catechin, rutin, quercetin, luteolin, baicaline, hesperidin and diosmin, have also the ability to prevent the aggregation of platelets through inhibition of fibrin synthesis that participates in the clot formation. Inhibition of this process is associated with chelation of Ca^{2+} ions that are necessary for proper operation of thromboplastin catalysing conversion of prothrombin into thrombin, which in turn, is responsible for the conversion of fibrinogen to fibrin (Kang *et al*., 2001).The protective effect of polyphenols is also related to the inhibition of hyaluronidase activity, the enzyme that is responsible for the enzymatic degradation of hyaluronic acid, as this acid is a building component of the blood vessel wall and dermis. Proven under *in vitro* conditions for quercetin, this function allows the reduction of swelling and puffiness by decreasing permeability of blood vessels. It was further demonstrated that an increase in vascular permeability is correlated with histamine release from mast cells and basophilic granulocytes in response to inflammations and allergies. *In vitro* studies showed that this process may be limited by the use of quercetin, kaempferol and myrecitin, as they have the ability to inhibit histamine (Middleton and Drzewiecki, 1984).

Antimicrobial activity of polyphenols. Polyphenols may also protect the skin against exogenous, pathogenic bacteria, fungi and viruses. This activity has been demonstrated *in vitro* for apigenin, quercetin and its glycosides, kaempferol, luteolin and its glycosides and catechin. It has been shown that these compounds may significantly inhibit or reduce the growth of bacteria (*Staphylococcus aureus*, *Staphylococcus albus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Bacillus subtilis*, *Micrococcus luteus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Salmonella typhimurium*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Stenotrophomonas maltophilia*), fungi (*Aspergillus niger*) and yeast (*Candida albicans*). Mechanism of this process is mainly associated with the ability to inhibit proteolytic enzymes activity by disturbing the synthesis of nucleic acids and the increased permeability of the cell wall to exogenous substances. In addition, antimicrobial properties of polyphenols assist in the preservation of cosmetics by protecting the physicochemical form of the product against secondary infections (Cowan, 1999; Cushnie and Lamb, 2005).

Other bioactivities of the polyphenols

It is also worth mentioning that polyphenols besides widely proven activities in human skin have also other bioactivities in animal and human health. The most important biological acivities of polyphenols are the ability to reverse specific age-related neurodegeneration, an ability to induce apoptosis in tumour cells and inhibit cancer cell proliferation, the ability to reduce the risk of cardiovascular disease, beneficial impact on the human gut microbiota and antipatogenic, antidiabetic and neuroprotective potentials (Cardona *et al*., 2013; McClain and Watson, 2013). Taking all this into account, we can conclude that the polyphenols are a group of plant metabolites with high importance on human health and beauty.

Summary

It should be remembered that the majority of polyphenolic compounds used in cosmetics is introduced in the form of plant extracts, which are a mixture of various compounds, frequently not having complete characteristics of their activity. Most of the available literature on the activity of polyphenols refers to the *in vitro* properties of specific polyphenols, most commonly in the form of aglycones. This fact allows to pose the question whether the mixture of polyphenolic active ingredients, either in forms of glycosides or aglycones, have a synergistic effect or more active is a single compound. Noteworthy is also the fact that in order to use a broad spectrum of biochemical properties of polyphenols in the skin, to reach the appropriate receptor they must be able to overcome the epidermal barrier. It is therefore important when assessing effectiveness of cosmetics containing polyphenolic compounds to apply both *in vitro* and *in vivo* or *ex vivo* studies.

Conflict of Interest

The authors declare that there are no conflicts of interest.

REFERENCES

Abdelouahab N, Heard CM. 2008. Dermal and transcutaneous delivery of the major glycoside constituents of *Harpagophytum procumbens* (Devil's Claw) *in vitro*. *Planta Med* **74**: 527–531.

Afanas'ev IB. 2007. Signaling functions of free radicals superoxide and nitric oxide under physiological and pathological conditions. *Mol Biotechnol* **37**: 2–4.

Ahmad N, Mukhtar H. 2004. Cytochrome p450: a target for drug development for skin diseases. *J Invest Dermatol* **123**: 417–425.

Anunciato TP, da Rocha Filho PA. 2012. Carotenoids and polyphenols in nutricosmetics, nutraceuticals, and cosmeceuticals. *J Cosmet Dermatol* **11**: 51–54.

Arct J, Bielenda B, Oborska A, Pytkowska K. 2003. The tea and its cosmetic application. *J Appl Cosmetol* **21**: 117–127.

Arct J, Gronwald M, Kasiura K. 2001. Possibilities for the prediction of an active substance penetration through epidermis. *IFSCCMagazine* **4**: 179–183.

Arct J, Oborska A, Mojski, M, Binkowska A, Idzikowska BS. 2002. Common cosmetic hydrophilic ingredients as penetration modifiers of flavonoids. *Int J Cosmet Sci* **24**: 357–366.

Arct J, Pytkowska K. 2008. Flavonoids as components of biologically active cosmeceuticals. *Clin Dermatol* **26**: 347–357.

Balasubramanian S, Eckert RL. 2007. Keratinocyte proliferation, differentiation, and apoptosis– differential mechanisms of regulation by curcumin, EGCG and apigenin. *Toxicol Appl Pharmacol* **224**: 214–219.

Baron JM, Höller D, Schiffer R, *et al*. 2001. Expression of multiple cytochrome p450 enzymes and multidrug resistance-associated transport proteins in human skin keratinocytes. *J Invest Dermatol* **116**: 541–548.

Behl CR, Char H, Patel SB, Mehta DB, Piemontese D, Malick AW. 1993. *In vivo* and *in vitro* skin uptake and permeation studies: critical considerations and factors which affect them. In: *Topical Drug Bioavailability, Bioequivalence and Penetration*, Shah VP, Maibach HI (eds). Plenum Press: New York, NY, USA; 225–259.

Bickers DR, Athar M. 2006. Oxidative stress in the pathogenesis of skin disease. *J Invest Dermatol* **126**: 2565–2575.

Bonina F, Lanza M, Montenegro L, *et al*. 1996. Flavonoids as potential protective agents photo-oxidative skin damage. *Int J Pharmac* **145**: 87–94.

Bos JD, Meinardi MM. 2000. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. *Exp Dermatol* **9**: 165–169.

Bravo L. 1998. Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. *Nutr Rev* **56**: 317–333.

Burdan F, Chałas A, Szumiło J. 2006. Cyclooxygenase and prostanoids – biological implications. *Postepy Hig Med Dosw* **60**: 129–141.

Cardona F, Andrés-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuño MI. 2013. Benefits of polyphenols on gut microbiota and implications in human health. *J Nutr Biochem* **24**: 1415–1422.

Cowan MM. 1999. Plants products as antimicrobial agents. *Clin Microbiol Rev* **12**: 564–582.

Cushnie TPT, Lamb AJ. 2005. Antimicrobial activity of flavonoids. *Int J Antimicrob Agents* **26**: 343–356.

Dangles O, Dufour C. 2008. Recent Advances on Polyphenol Research, Daayf F, Lattanzio V. Wiley-Blackwell: Oxford; 67–87.

De Groot H, Rauen U. 1998. Tissue injury by reactive oxygen species and the protective effects of flavonoids. *Fundam Clin Pharmacol* **12**: 249–255.

Dewick PM. 1995. The biosynthesis of shikimate metabolites. *Nat Prod Rep* **12**: 579–607.

Diniz A, Escuder-Gilabert L, Lopes NP, Gobbo-Neto L, Villanueva-Camañas RM, Sagrado S, Medina-Hernández MJ. 2007. Permeability profile estimation of flavonoids and other phenolic compounds by biopartitioning micellar capillary chromatography. *J Agric Food Chem* **17**: 8372–8379.

Fang JY, Hung CF, Hwang TL, Wong WW. 2006. Transdermal delivery of tea catechins by electrically assisted methods. *Skin Pharmacol Physiol* **19**: 28–37.

Gil B, Sanz MJ, Terencio MC, Ferrandiz ML, Bustos G, Paya M. 1994. Effects of flavonoids on Naja naja and human recombinant synovial phospholipases A_2 and inflammatory responses in mice. *Life Sci* **54**: 333–338.

Gonzalez FJ, Tukey RH, Brunton LL, Lazo JS, Parker KL. 2006. Drug metabolism. In Goodman and Gilman's the pharmacological basis of therapeutics. Eleventh ed. Medical Publishing Division: New York, McGraw-Hill; 71–91.

Guerrero JA, Lozano ML, Castillo J. 2005. Flavonoids inhibit platelet function through binding to the thromboxane A_2 receptor. *J Thromb Haemost* **3**: 369–377.

Gulliksson M, Brunnström A, Johannesson M, *et al*. 2007. Expression of 15-lipoxygenase type-1 in human mast cells. *Biochim Biophys Acta* **1771**: 1156–1165.

Harborne JB. 1986. Nature, distribution, and function of plant flavonoids. In Plant Flavonoids in Biology and Medicine, Cody V, Middleton E, Harborne JB (eds). Alan R. Liss: New York; 15–24.

Harborne JB. 1989. Methods in plant biochemistry. In Plant Phenolics. Academic Press: London; 1–28; 283-323.

Herschman HR. 1996. Prostaglandin synthase 2. *Biochim Biophys Acta* **1299**: 125–140.

Hou Z, Lambert JD, Chin KV, Yang CS. 2004. Effects of tea polyphenols on signal transduction pathways related to cancer chemoprevention. *Mutat Res* **555**: 3–19.

Jasiński M, Mazurkiewicz E, Rodziewicz P, Figlerowicz M. 2009. Flawonoidy- budowa, właściwości i funkcja ze szczególnym uwzględnieniem roślin motylkowatych. *Biotechnol* **2**: 81–94.

Jung EG, Steche J. 1972. Percutaneous penetration of hydroxyethylrutosides. *Eur J Clin Pharmacol* **4**: 182–184.
Kang WS, Chang KH, Chung JH. 2001. Antiplatelet activity of green tea catechins is mediated by inhibition of cytoplasmic calcium increase. *J Cardiovasc Pharmacol* **38**: 875–884.
Kanikkannan N, Kandimalla K, Lamba SS, Singh M. 2000. Structure-activity relationship of chemical penetration enhancers in transdermal drug delivery. *Curr Med Chem* **7**: 593–608.
Katiyar SK, Matsui MS, Mukhtar H. 2000. Ultraviolet-B exposure of human skin induces cytochromes P450 1A1 and 1B1. *J Invest Dermatol* **114**: 328–333.
Kim D, Park J, Kim J, *et al*. 2006. Flavonoids as mushroom tyrosinase inhibitors: a fluorescence quenching study. *J Agric Food Chem* **54**: 935–941.
Kogan A, Garti N. 2006. Microemulsions as transdermal drug delivery vehicles. *Adv Colloid Interface Sci* **16**: 123–126.
Korkina L, De Luca Ch, Pastore S. 2012. Plant polyphenols and human skin: friends or foes. *Ann NY Acad Sci* **1259**: 77–86.
Korkina L, Pastore S, De Luca C, Kostyuk V. 2008. Metabolism of plant polyphenols in the skin: beneficial versus deleterious effects. *Curr Drug Metab* **9**: 710–729.
Korkina LG, Mikhal'chik EV, Suprun MV, Pastore S, Dal Toso R. 2007. Molecular mechanisms underlying wound healing and anti-inflammatory properties of naturally occurring biotechnologically produced phenylpropanoid glycosydes. *Cell Mol Biol* **53**: 78–83.
Kostelac D, Rechkemmer G, Briviba K. 2003. Phytoestrogens modulate binding response of estrogen receptors alpha and beta to the estrogen response element. *J Agric Food Chem* **51**: 7632–7635.
Kwak J, Park J, Lee J, *et al*. 2005. Inhibition of enzyme activities and the antiwrinkle effect of polyphenol isolated from the persimmon leaf (*Diospyros kaki folium*) on human skin. *Dermatol Surg* **31**: 848–855.
Lee JL, Mukhtar H, Bickers DR, Kopelovich L, Athar M. 2003. Cyclooxygenases in the skin: pharmacological and toxicological implications. *Toxicol Appl Pharmacol* **192**: 294–306.
McClain GE, Watson RR. 2013. The role of polyphenols in skin health. Bioactive Dietary Factors and Plant Extracts in Preventive DermatologyNutrition and Health; Humana Press, Springer Science Business Media, New York 2013, ISBN 978-1-62703-166-0, 169–175.
Marti-Mestres G, Mestres JP, Bres J, Martin S, Ramos J, Vian L. 2007. The *in vitro* percutaneous penetration of three antioxidant compounds. *Int J Pharm* **331**: 139–144.
Masaki H. 2010. Role of antioxidants in the skin: anti-aging effects. *J Dermatol Sci* **58**: 85–90.
Merfort I, Heilmann J, Hagedorn-Leweke U, Lippold BC. 1994. *In vivo* skin penetration studies of camomile flavones. *Pharmazie* **49**: 509–511.
Middleton E, Drzewiecki G. 1984. Flavonoid inhibition of human basophil histamine release stimulated by various agents. *Biochem Pharmacol* **33**: 3333–3338.
Mucha P, Budzisz E, Rotsztejn H. 2013. The inhibitory effects of polyphenols on skin UV immunosuppression. *Postepy Hig Med Dosw* **67**: 358–362.
Naik A, Kalia YN, Guy RH. 2000. Transdermal drug delivery: overcoming the skin's barrier function. *Pharm Sci Tech Today* **3**: 318–325.
Nakamura Y, Ishii T, Abe N, Murata Y. 2014. Thiol modification by bioactivated polyphenols and its potential role in skin inflammation. *Biosci Biotechnol Biochem* **78:** 1067–1070.
Nichols JA, Santosh K, Katiyar SK. 2010. Skin photoprotection by natural polyphenols: anti-inflammatory, anti-oxidant and DNA repair mechanisms. *Arch Dermatol Res* **302**: 71–83.
Oborska A, Arct J. 2010. Skin permeation of flavonoids - model approach. *SÖFW-Journal* **136**: 22–28.
Oesch F, Fabian E, Oesch-Bartlomowicz B, Werner C, Landsiedel R. 2007. Drug-metabolizing enzymes in the skin of man, rat, and pig. *Drug Metab Rev* **39**: 659–698.
OyetakinWhite P, Tribout H, Baron E. 2012. Protective mechanisms of green tea polyphenols in skin. *Oxid Med Cell Longev,* doi:10.1155/2012/560682.
Pastore S, Lulli D, Fidanza P, *et al*. 2012. Plant polyphenols regulate chemokine expression and tissue repair in human keratinocytes through interaction with cytoplasmic and nuclear components of epidermal growth factor receptor system. *Antioxid Redox Signal* **16**: 314–328.
Pastore S, Mascia F, Mariani V, Girolomoni G. 2008. The epidermal growth factor receptor system in skin repair and inflammation. *J Invest Dermatol* **128**: 1365–1374.
Pastore S, Potapovich A, Kostyuk V, *et al*. 2009. Plant polyphenols effectively protect HaCaT cells from ultraviolet C-triggered necrosis and suppress inflammatory chemokine expression. *Ann N Y Acad Sci* **1171**: 305–311.
Portugal M, Barak V, Ginsburg I, Kohen R. 2007. Interplay among oxidants, antioxidants, and cytokines in skin disorders: present status and future considerations. *Biomed Pharmacother* **61**: 412–422.
Potapovich AI, Lulli D, Fidanza P, *et al*. 2011. Plant polyphenols differentially modulate inflammatory responses of human keratinocytes by interfering with activation of transcription factors NFκB and AhR and EGFR-ERK pathway. *Toxicol Appl Pharmacol* **255**: 138–149.
Quideau S, Deffieux D, Douat-Casassus C, Pouységu, L. 2011. Plant polyphenols: chemical properties, biological activities, and synthesis. *Angew Chem Int Ed* **50**: 586–621.
Rhein LD, Fluhr JW. 2010. Aging skin: current and future therapeutic strategies. Allured Business Media: USA; 182–184, 225-240,
Rice-Evans CA, Miller NJ, Paganga G. 1997. Antioxidant properties of phenolic compounds. *Trends Plant Sci* **2**: 152–159.
Saija A, Trombetta D, Tomaino A, *et al*. 1998. *In vitro* evaluation of the antioxidant activity and biomembrane interaction of the plant phenols oleuropein and hydroxytyrosol. *Int J Pharmacol* **166**: 123–133.
Schwab JM, Schluesener HJ, Meyermann R, Serhan CN. 2003. COX-3 the enzyme and the concept: steps towards highly specialized pathways and precision therapeutics? *Prostaglandins Leukot Essent Fatty Acids* **69**: 339–343.
Subedi RK, Oh SY, Chun MK, Choi HK. 2010. Recent advances in transdermal drug delivery. *Arch Pharm Res* **33**: 339–351.
Thring TS, Hili P, Naughton DP. 2009. Anti-collagenase, anti-elastase and anti-oxidant activities of extracts from 21 plants. *BMC Complement Altern Med* **4**: 27–31.
Ververidis F, Trantas E, Douglas C, Kretzchmar G, Panopoulos N. 2007. Biotechnology of flavonoids and other phenylpropanoid-derived natural products. *Biotechnol J* **2**: 1214–1234.
Villard PH, Sampol E, Elkaim JL. 2002. Increase of CYP1B1 transcription in human keratinocytes and HaCaT cells after UV-B exposure. *Toxicol Appl Pharmacol* **178**: 137–143.
Wright TI, Spencer JM, Flowers FP. 2006. Chemoprevention of nonmelanoma skin cancer. *J Am Acad Dermatol* **54**: 933–946.
Xue YL, Miyakawa T, Hayashi Y, *et al*. 2011. Isolation and tyrosinase inhibitory effects of polyphenols from the leaves of persimmon, *Diospyros kaki*. *J Agric Food Chem* **59**: 6011–6017.
Yoon JH, Baek SJ. 2005. Molecular targets of dietary polyphenols with anti-inflammatory properties. *Yonsei Med J* **46**: 585–596.