International Journal of
Cosmetic Science

*International Journal of Cosmetic Science*, 2015, **37**, 455–464 doi: 10.1111/ics.12218

Review Article

# Polyphenols as active ingredients for cosmetic products

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Received 5 December 2014, Accepted 7 February 2015

**Keywords:** polyphenols, antioxidant activity, photoprotective activity, release, skin delivery, interactions

## Synopsis

Polyphenols are secondary plant metabolites with antioxidant, anti-inflammatory and anti-microbial activity. They are ubiquitously distributed in the plant kingdom; high amounts contain, for example, green tea and grape seeds. Polyphenolic extracts are attractive ingredients for cosmetics and pharmacy due to their beneficial biological properties. This review summarizes the effects of polyphenols in the context of anti-ageing activity. We have explored *in vitro* studies, which investigate antioxidant activity, inhibition of dermal proteases and photoprotective activity, mostly studied using dermal fibroblasts or epidermal keratinocytes cell lines. Possible negative effects of polyphenols were also discussed. Further, some physico-chemical aspects, namely the possible interactions with emulsifiers and the influence of the cosmetic formulation on the skin delivery, were reported. Finally, few clinical studies, which cover the anti-ageing action of polyphenols on the skin after topical application, were reviewed.

## Résumé

Les polyphénols sont des métabolites secondaires des plantes ayant une activité anti-oxydante, anti-inflammatoire et antimicrobienne. Ils sont distribués partout dans le règne végétal; par exemple, le thé vert et les pépins de raisin contiennent des quantités élevées. Les extraits polyphénoliques sont des ingrédients intéressants pour les produits cosmétiques et la pharmacie en raison de leurs propriétés biologiques bénéfiques. Cette revue résume les effets des polyphénols dans le contexte de l'activité anti- vieillissement. Nous avons exploré les études *in vitro*, qui étudient l'activité anti-oxydante, l'inhibition de protéases du derme et l'activité photoprotectrice, et qui sont principalement étudiées en utilisant des lignées cellulaires des fibroblastes dermiques ou de kératinocytes épidermiques. Les effets négatifs possibles de polyphénols sont également discutés. En outre, certains aspects physico-chimiques, à savoir les interactions possibles avec des émulsifiants et l'influence de la formulation cosmétique sur la biodisponibilité au niveau de la peau, sont signalés. Enfin, quelques études cliniques, qui couvrent l'action antivieillissement des polyphénols sur la peau après l'application topique ont été examinées.

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## Introduction

According to the current knowledge, UV irradiation and oxidative stress are the main causes of extrinsic (premature) ageing and some cutaneous damages and diseases as skin cancer [1–5]. Oxidative stress is provoked by an excess of reactive oxygen species (ROS). Under normal conditions, the endogenic antioxidant system of the skin is very effective. It contains enzymes, such as glutathione peroxidase, glutathione reductase, catalase and superoxide dismutase, which degrade hydrogen peroxide, lipid hydroperoxides and superoxide. Non-enzymatic antioxidants are, for example, skin's own L-ascorbic acid in the aqueous phase, glutathione in the cellular compartment, α-tocopherol in membranes and ubiquinol in mitochondria [4, 5]. When the organism is exposed to oxidative stress, the effectiveness of the endogenic antioxidant system is diminished. For example, after irradiation of skin fibroblasts with UVA, the activity of catalase and superoxide dismutase decreases [5]. ROS initiate chain reaction of lipid peroxidation in the cell membranes and intrude into the signal transduction pathways that are involved in the expression of genes, which regulate collagen metabolism [4–6]. For example, due to some signal cascades, an overexpression of matrix metalloproteinases (MMP) occurs. MMPs include, inter alia, MMP-1 (collagenase), MMP-3 (stromelysin) and MMP-9 (gelatinase). These enzymes catalyse the degradation of the corresponding proteins. The expression of MMPs occurs both in epidermal keratinocytes and in dermal fibroblasts; therefore, these skin layers are particularly susceptible to the sun damage [4, 5]. The genetic material is often damaged by UV irradiation as DNA can directly absorb UVB light. This facilitates the dimerization of pyrimidine bases, which can cause mutations and errors in DNA replication. Furthermore, UVA can also inhibit DNA repair [5]. This effect and the described activation of MMPs and lipid oxidation increase the probability of cancer development and premature skin ageing.

To support the endogenic antioxidant system, antioxidants can be supplied either by the diet or applied directly to the skin. They can scavenge ROS and inactivate MMP what results in a normalized production of skin structural proteins [7]. Hence, some preventive or reparative effects could be achieved in this way. Polyphenols are plant compounds with high antioxidative activity making them attractive as ingredients for cosmetics [8]. The present paper reviews the recently published literature data describing effects of polyphenols on the human skin. Despite the fact that most studies show beneficial effects of polyphenols, there are some *in vitro* investigations showing possible negative impacts, these

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studies have been also discussed. Furthermore, important physicochemical aspects of polyphenols formulation to cosmetic products as skin permeation and physical properties of formulations have been described.

## Structure and sources of polyphenols

The term 'polyphenols' includes a large group of substances, which all have more than one phenolic hydroxyl group, bounded to one or more benzene ring systems [6]. Flavonoids are the main group of polyphenols. They include, inter alia, such classes as flavanoles, flavones, anthocyanidins and isoflavones, presented in Fig. 1. Flavonoids which possess characteristic $C_6$-$C_3$-$C_6$ structures, having a six-member oxygen heterocycle (C). Flavan-3-oles (also called catechins) have completely saturated heterocycle, they can be esterified at the 3′-hydrohyl group [as e.g. epigallocatechin-3-gallate (EGCG)]. Flavones contain a ketone group in their unsaturated heterocycle (e.g. quercetin). The heterocycle of pigments anthocyanidins is a pyrylium cation, giving them their deep colours what depends on the pH and presence of other substances as metal ions (e.g. blue-violet delphinidin). Isoflavones have their B-ring in a different position on the oxygen heterocycle as other flavonoids. Figure 1 also presents the structural formula of resveratrol, a representative of the stilbene group, having a $C_6$-$C_2$-$C_6$ skeleton. Phenolic compounds are often esterified with sugars or organic acids resulting in a complex spectrum of over 5000 compounds naturally occurring in plants.

The chemical structure of polyphenolic compounds causes their reducing properties, which allow them to act as antioxidants and free radical scavengers. The antioxidant activity of flavonoids is essentially determined due to substitutions on rings B and C, for example the number and positions of hydroxyl groups in the B-ring as well as double bonds and substitutions in the ring C [9]. The major sources of polyphenols are fruits and berries, vegetables, spices, oil seeds and tea [10]. Polyphenols are secondary plant metabolites, produced only in small amounts and not in the primary energy metabolism of plants; their functions in the plant are, for example, the protection of the plant against UV radiation or vermin [6].

One of the best sources of phenolic antioxidants is tea (*Camellia sinensis* L.), especially green tea but also black tea, oolong tea and white tea are excellent polyphenol suppliers and possess great antioxidant properties. The major polyphenols in tea are flavan-3-ols, particularly epigallocatechin-3-gallate (EGCG), epigallocatechin, epicatechin, epicatechin-3-gallate [11, 12]. Besides tea, grape (*Vitis vinifera* L.), one of the largest fruit crops in the world, is an

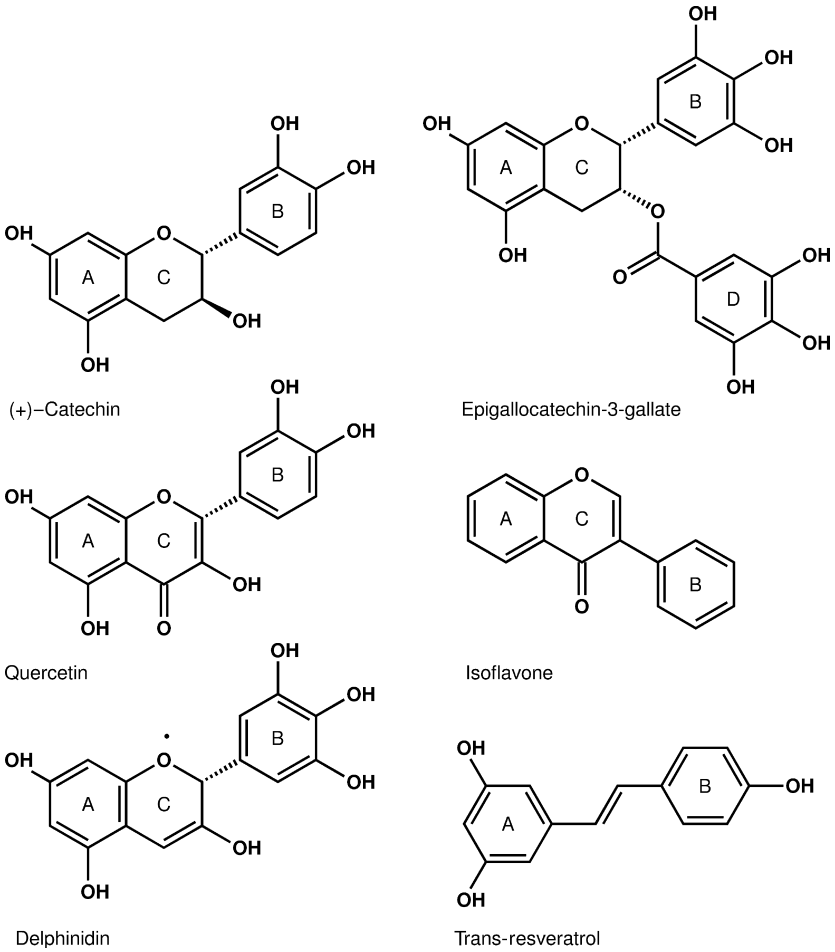


**Figure 1** Representatives of flavanols (catechin, epigallocatechin gallate), flavones (quercetin), isoflavones (isoflavone), anthocyanidins (delphinidin), and stilbenes (trans-resveratrol).


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important source of polyphenols. The antioxidant activity of grapes seems to be depended on the colour of the berries; dark fruits have higher antioxidant capacity than the white ones, because the content of anthocyanins and flavonoids increases with increasing colour intensity of grapes [13].

Olives, sesame and various other oilseeds such as sunflower, as well as the cold pressed oils derived thereof contain polyphenolic compounds such as flavonoids and phenolic acid [10, 14]. Pistachio nuts are also rich on phenolic compounds; the most abundant polyphenols are anthocyanins, which are mainly located in the skins [15].

Woods, such as oak (*Quercus robur)*, pine (*Pinus maritime*) or cinnamon (*Cinnamomum zeylanicum*), particularly the barks, contain phenolic substances with high antioxidant capacity, mainly catechin, epicatechin, procyanidins and phenolic acids [16, 17]. The oak leaves are also rich on polyphenols. Ellagic acid, rutin and hyperoside were identified in the study of Almeida *et al.* [18], who demonstrated also the possibility of the topical application of oak leaf extract.

Tropical fruits such as pineapple, passion fruit, acerola, pomegranate or mangosteen are also important sources of phenolic compounds, which are often concentrated in the peels as their function is the protection of the fruits against UV [19–22]. In particular, mangosteen has gained more and more attention in the last year as so-called super fruit; it has been used in Southeast Asia for centuries in the treatment of skin infections, mycosis, inflammation and other diseases. The high amounts of xanthone derivatives, mainly concentrated in the pericarp, are responsible for the antioxidant capacity and the healing power of mangosteen [22].

Interesting sources for polyphenols are wastes and by-products from food production, for example grape or apple pomace, coffee residues and others. The grape skins, seeds and stems and waste products produced during wine and grape juice processing, are rich in polyphenols. They contain flavonoids, phenolic acids and stilbenes [8, 23, 24]. For example, in red grapes, catechin and epicatechin are located mostly in seeds; quercetin, rutin and resveratrol are found in grape skin extracts [25]. The polyphenols of apple, including catechins, hydroxycinnamates, phloretin glycosides, quercetin glycosides and procyanidins, are predominantly localized in the peels and are faintly extracted into the juice, making the apple pomace to a good source of polyphenols [26]. High phenolic contents in other industrial plant residues, for example pulp, seeds and peel of acerola, passion fruit and pineapple have been also reported [27]. The major polyphenols identified in pineapple peels are gallic acid, catechin, epicatechin and ferrulic acid [19].

The extraction of polyphenols from by-products of food production can be promising for the cosmetic industry, which is always searching on new sustainable and cost-effective sources for functional ingredients.

## *In vitro* activity

Table I summarizes the biological activities of polyphenols which are most relevant for their topical application.

### Antioxidant properties

Topical application of antioxidative active substances can support the skin's own antioxidant system against oxidative stress and could protect the skin against photoageing over a long term. The antioxidant properties of polyphenols from plant material have been described extensively in the literature [8, 9]. The most common approach to investigate the antioxidant activity of substances *in vitro* is their free radical scavenging activity; the samples are mixed with stable radicals, and the rate of the radical degradation is measured, for example by spectrophotometry [8, 25, 27, 31]. These methods reflect the possible protective action of plant extracts on the skin against ROS provoked, for example by UV irradiation.

The inhibition of lipid oxidation, measured in liposomal models, reproduces the protective action of polyphenols on the cell membranes [8]. The extension of the induction period of oil oxidation [29, 30, 32] represents the possible antioxidant action of polyphenols in the formulation during storage.

Antioxidant activity of plant extracts often correlates with the total phenolic content [16, 49]. However, the polyphenol profile also determines the effectiveness of extracts, as the activity of individuals substances varies strongly [30], caused by the differences in the chemical structure [9]. For example, the antioxidant activity of rutin fatty acid esters in lipid systems increases with their lipophilicity [32]. The high antioxidative activity of grape or tea extracts is derived from a combination of several active substances, which results in an increased activity due to some synergistic effects [25].

### Anti-collagenase and anti-elastase activity

Phenolic extracts are found to inhibit the activity of proteinases, which catalyse the degradation of skin proteins, such as collagen and elastin. Collagen in the dermis is responsible for the firmness, elastin fibres lend the elasticity. An excessive ROS formation provokes the expression of collagenase (MMP-1) and elastase, leading to an accelerated degradation of corresponding proteins.

Thring *et al.* determined anti-collagenase, anti-elastase and antioxidant activities of 21 plant extracts and correlated them with the total phenolic content. The white tea extract showed the highest inhibitory activity against both enzymes as well as the highest antioxidant activity and phenolic content [33].

Lee *et al.* [35] isolated a phenolic substance from *Areca catechu* L., which effectively inhibited elastase and hyaluronidase – an enzyme, which catalyses the degradation of hyaluronic acid in the extracellular matrix in the dermis – and suggested its anti-ageing effect. Phenolic compounds, isolated from *Malus dounteri* A. Chev., a Taiwanese indigenous plant, also exhibited anti-elastase and anti-MMP-1 activity, determined in human skin fibroblast cells. The most potent enzyme inhibitors were phloretin, 3-hydro phloretin and quercetin [36]. Aldehyde polycondensates of (+)-catechin were demonstrated to have superior anti-collagenase and anti-elastase activities in comparison with the catechin monomer [37]. In heat-stimulated human dermal fibroblasts, EGCG inhibited MMP-1 expression, suggesting that EGCG can prevent heat shock-induced skin ageing [44].

### Protection against UV damages and oxidative stress

The ability of polyphenols to act as photoprotectors is also of importance for cosmetic applications. The sun protection factors (SPF) of flavonoids, stilbenes and hydroxycinnamic acid derivatives, determined in [50], were from 7 to 29, corresponding to 'minimal' (SPF from 2 to 12) and 'moderate' (SPF from 12 to 30) sun protection properties. Moreover, the possibility of preventing or reducing UV-induced photodamages makes the plant polyphenols to relevant topical ingredients. In the recent review, the photoprotection properties of polyphenols have been summarized [51].

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**Table I** *In vitro* activities of polyphenols

| | Activity | Reference |
|---|---|---|
| Cell-free systems | | |
| Antioxidant activity | Free radical scavenging capacity, measured by the inhibition of stable radicals: DPPH (2,2-diphenyl-1-picrylhydrazyl), ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)), peroxynitrite ($ONOO^-$), superoxide anion ($O^{-2}$), hydroxyl radicals | [8, 9, 16, 25, 27–31] |
| | Oxygen radical absorbance capacity (ORAC) assay; superoxide dismutase (SOD) assay; ferric reducing antioxidant potential (FRAP) assay | [16] |
| | Inhibition of lipid oxidation (liposomes, thermal acceleration of oils) | [8, 27, 29, 30, 32] |
| Inhibition of skin's enzymes | Anti-elastase activity | [33–37] |
| | Anti-collagenase activity | [33, 34, 37] |
| | Anti-hyaluronidase activity | [35] |
| Cell cultures | | |
| Prevention of oxidative DNA-damages, increasing cell viability, reduction of intracellular ROS | UVB-Irradiated human HaCaT keratinocytes, comet assay | [31, 38, 39] |
| | Fibroblasts stressed with $H_2O_2$ | [40] |
| | UV-irradiated normal human epidermal keratinocytes (NHEK) | [41] |
| Anti-inflammatory activity | Inhibitory effects on the release of inflammatory mediators such as IL-6, IL-8, prostaglandin-E2 in HaCaT cells, NHEK, fibroblasts | [34, 39, 41, 42] |
| Inhibition of UV or heat-induced enzyme release | Activity of MMP1, MMP2, MMP3, hyaluronidase gene expression in human dermal fibroblasts | [36, 43, 44] |
| Anti-cancer activity | Reduced viability and increased cell death of human skin cancer cell lines | [45] |
| | Decreased melanoma cell viability | [46] |
| Anti-microbial activity | Anti-bacterial, anti-fungal, antiviral activity | [8, 28, 47, 48] |

A number of studies describe the effects of polyphenolic extracts on human cells and UV-irradiated cells. The pre-treatment of HaCaT keratinocytes with polyphenols or phenolic extracts leads to a decreased intracellular ROS formation, induced by UVB or hydrogen peroxide. In addition, a prevention of DNA damage, for example attenuated cyclobutane pyrimidine dimers formation, and prevention of cell apoptosis could be observed [31, 38, 39].

The treatment of normal human dermal fibroblasts (NHDF) with *Epilobium angustifolium* polyphenol extract prior to UV irradiation led to the down-regulation of UV-induced release of MMP-1 and MMP-3, and of the gene expression of the hyaluronidase 2; the viability of the senescent NHDF was also improved due to the extract treatment [43].

Strawberry extract containing mainly flavonoids and anthocyanins, protected dermal fibroblasts from oxidative stress induced through $H_2O_2$. Pre-incubation with the strawberry extract resulted in an increased cell viability, decreased intracellular amount of ROS and a reduction of membrane lipid peroxidation and DNA damage [40].

Potapovich *et al.* [41] showed that the post-treatment of normal human epidermal keratinocytes (NHEKs) after UV exposition with plant polyphenols (resveratrol, quercetin, verbascoside) was effective to abolish the overproduction of peroxides and inflammatory mediators.

These studies suggest that polyphenolic extracts can be useful ingredients for both sunscreens and after sun cosmetic products.

As photodamages can lead to the formation of skin cancer, the properties described above suggest the positive effects of plant polyphenols during anti-cancer therapy. Polyphenols have been shown to have anti-carcinogenic effects in several skin tumour models [45, 46], but only few clinical studies have been realised. The assignability of *in vitro* and *in vivo* results is the central point of anti-cancer research. This situation and the role of polyphenols during the therapy or cancer prevention have been successively analysed [52–54].

### Effect of polyphenols on the cell viability

The numerous positive effects of polyphenols described above lead to their increased use as cosmetic ingredient or food additive. However, some recent studies have been published which suggest that polyphenols can exert cytotoxic effects. Concerning this matter, there is contradictoriness in the recent literature.

For example, Lu *et al.* asserted that antioxidants and particularly EGCG and green tea extract induced cell death and DNA damage in human lung and skin cells. The researchers explain a reductive mechanism of antioxidant action as much more dangerous for DNA than the oxidation through ROS. EGCG is claimed to induce DNA double-strand breaks and apoptosis in normal cells and to enhance the mutation frequency. Moreover, it is also claimed to slightly increase the lung cell cancer viability at low concentrations [55]. Furthermore, propolis, a bee drug, which have been used in the traditional medicine since long times, was reported to reveal anti-proliferative and cytotoxic action followed by mild cell necrosis in the fibroblasts assay by highly dosed application (over 0.01 % (w/v)) [56]. Moreover, the group of Fox *et al.* identified 22 antioxidants as genotoxic compounds. However, the investigated substances exhibited various grade of toxicity. For example, resveratrol and genistein did not cause mutagenesis, which is a major side effect of conventional anti-cancer drugs, but killed multidrug-resistant cancer cells, which still make these polyphenols to attractive candidates for improved chemotherapeutic agents [57].

Much more published studies describe that polyphenols did not affect the cell viability negatively. For example, the polyphenol-rich strawberry extract, investigated by [40], was proved to not provoke any cytotoxic effects. Negrao *et al.* studied the effects of catechin on angiogenic and inflammatory processes. Treatment with catechin increased viability and decreased apoptosis and proliferation of endothelial cells and vascular smooth muscle cells *in vitro* [58]. Chamcheu *et al.* [59] demonstrated that delphinidin significantly


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enhanced keratinocyte differentiation of NHEKs, but do not induce their apoptosis.

These contradictory findings require more attention and more appropriate further investigations, because of the extensive use of polyphenols in many areas, also in cosmetic or pharmacy.

## Cosmetic application of polyphenols

The beneficial effects of polyphenols as functional ingredients have attracted considerable attention of the pharmaceutical and cosmetic industry in recent years. As a consequence, many skin care products or so-called cosmeceuticals have been developed based on polyphenol-enriched plant extracts. To exert their designated biological activities, topically applied substances have to be able to be released from the formulation, to reach the skin and finally to overcome the *Stratum Corneum* barrier and penetrate into the epidermis and dermis. The release of active substances and further skin permeation depends on the molecule properties such as molecular weight and lipophilicity, but also on the vehicle formulation [60, 61]. The formulations have to be chemically, physically and microbiologically stable to assure the stability and deliverability of active substances to the target skin layers.

### Effects of polyphenols on physical properties of formulations

To assure a good migration of polyphenols into the skin, they should not precipitate in the used vehicle formulation. Due to the poor solubility, some polyphenols rapidly precipitate in water, but surfactants such as polyoxyethylenesorbitan monolaurate or block copolymers promote their solubilization, as shown for flavonoids naringenin, rutin and quercetin [62, 63].

Emulsions are the most convenient type of topical formulations because of their solubilizing capacity for both lipophilic and hydrophilic ingredients. Emulsions are heterogeneous systems consisting of two immiscible phases (water and oil phases); one phase is dispersed in the other and stabilized with an emulsifier [64].

The physical location of the antioxidants in emulsions is an important factor of their activity. As reported by Richards *et al.*, non-ionic surfactant micelles affected the solubilization of phenolic antioxidants depending on their polarity, namely non-polar substances were less solubilized than polar [65]; and confirmed the existence of 'polar paradox' what means that there is a higher effectiveness of non-polar antioxidants in water continuous emulsions and vice versa [66]. However, in another study, the antioxidant activity of alkyl gallates in O/W emulsions (oil-in-water), stabilized with sodium dodecyl sulphate or polyoxyethylene cetyl ether, did not increase with decreasing polarity of phenolics [67], which lead to a suggestion, that the 'polar paradox' is limited to the emulsions containing emulsifiers with properties similar to phospholipids.

The incorporation of polyphenols into emulsions can influence their rheological properties as well as their stability, particularly, the decrease of viscosity could be observed [68]. The reasons of this effect are not completely understood up to now. Besides the obvious dilution effect, one reason could be based on interactions of polyphenols with emulsifiers. There are some references describing interactions of polyphenols with proteins [69, 70], usually involving reversible complexation due to non-covalent forces (hydrogen bonding, hydrophobic bonding, van der Waals forces), or irreversible aggregation with formation of covalent bonds (due to oxidation, nucleophilic addition process or enzymatic transformations). Studies describing interactions between polyphenols and other macromolecules such as polysaccharides, obviously involving similar mechanisms, can be also found in literature [69]. Some ionic polysaccharides such as xanthan or pectin are reported to inhibit protein–phenolic interactions, probably by building a gel-like network in solutions. Xanthan can form hydrophobic pockets and is able to encapsulate and complex polyphenols. Furthermore, a molecular association in solution between carbohydrates and polyphenols is also possible [69, 71, 72]. These interactions could explain the alteration of viscosity of the formulation, if it contains proteins or polysaccharides.

Interactions of polyphenols with non-ionic or anionic surfactants, which are commonly used in cosmetic emulsions, are described rarely. Stöckmann *et al.* studied non-ionic micelles of Brij 58 (polyoxyethylene (20) cetyl ether), in which some derivatives of hydroxybenzoic acids were emulsified. The diffuse environment, constructed of the oxygen atoms of the polyoxyethylene chains in Brij 58, attracted phenolics, allowing them to penetrate deeper into the polyoxyethylene environment. In contrast, in the anionic micelles, gallates were oriented with their hydroxyl groups closely to the polar head groups of sodium dodecyl sulphate [67]. This arrangement could influence the effectiveness of emulsifiers and also lead to the alteration of the viscosity of emulsions.

On the other hand, it was reported, that polyphenols show slight surface active properties. For example, catechin can accumulate at the air/water interface and decrease the surface tension. In the oil-in-water emulsions, gallic acid, catechin and quercetin decreased the surface tension, which lead in some cases to alteration of droplet sizes of emulsions, namely the addition of catechin caused bigger oil droplets, whereas quercetin improved the dispersion state of emulsion [73].

For some flavonoids, particularly for rutin, a stabilizing effect on emulsions was described [74]. Flavonoids could be adsorbed into the oil–water interface, and insoluble particles acted as stabilizers by formation of Pickering emulsions [75]. This stabilizing ability was found to be dependent on the pH-value, for example rutin promoted a formation of tetradecane emulsions with smaller droplet sizes at smaller pH values [74].

Due to their antioxidant properties, polyphenols can improve the oxidative stability and storage stability of emulsions [73]; these effects are intensified due to ability of polyphenols to adsorb on the oil–water interface and even to replace interfacial molecules, particularly proteins, as has been shown for rutin-containing O/W emulsions [76].

Some authors report the incorporation of polyphenols into solid carrier, in order to increase the solubility of polyphenols in aqueous media as well as to improve their stability in the topical formulation. For example, the formulation of quercetin to polyvinylpyrrolidone solid dispersions considerably could improve the solubility of quercetin as well as its antioxidant activity [77]. The encapsulation of quercetin in tristearin microparticles using phosphatidylcholine as emulsifier decreased its photodegradation in the topical formulation and considerably improved the storage stability [78].

### Effect of formulations on the release and skin permeation of polyphenols

An important aspect for the topical formulations is the ability of active substances to achieve the target skin layer, where their biological action could be exerted. In case of polyphenols as anti-ageing agents, the target skin layers are the dermis and the epidermis. As described, for example for resveratrol, the epidermis con-

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tains some polyphenol binding sites, so that resveratrol exert the protective action after linking on these sites [79]. A permeation of cosmetic ingredients through the skin into the vascular system, however, is not desired. The investigation of skin permeation behaviour is usually carried out *in vitro* by means of diffusion cells using excised human or animal skin [80].

A part of the complex process of permeation via the skin is the release of substances from the formulation. The faster the release rate, the earlier the substance can achieve the skin and penetrate into it. In some cases, the permeation and release coefficients can correlate [81]. As the release rate is an important factor for the evaluation of active ingredients in different cosmetic products, it might be sufficient to investigate primarily the release rate. For example, the liberation of rutin from semisolid systems is mainly dependent on the emulsion components. Urea and isopropanol impede the release of rutin from the formulations. In contrast, the presence of propylene glycol promotes the rutin release [61].

The skin permeation behaviour of some individual polyphenols using pig skin was investigated in our recent study [81]. It could be shown that the permeation rates depend on the molecular weight and polarity. The smallest and the most hydrophilic protocatechuic acid exhibited the highest permeation rates, followed by catechin, resveratrol, rutin, quercetin and EGCG, respectively. High amounts of polyphenols were observed in the epidermis and dermis. Similar findings were obtained in other studies. In penetration tests of EGCG and quercetin from green tea and *Gingko biloba* via the excised human skin [82], the majority of quercetin was quantified in the viable epidermis, but the amount of EGCG in the *Stratum Corneum* was higher than the concentrations in viable epidermis and in the dermis. Abla *et al.* studied delivery of antioxidants with different polarity from the propylene glycol vehicle via porcine ear skin. Polyphenols, which are more polar (catechin, resveratrol and curcumin), were mostly concentrated in the *Stratum Corneum* whereas less polar retinol accumulated in the underlying layers of the skin [83]. Similarly, after the *in vitro* permeation study using guinea pig skin and Yucatan micropig skin, hydrophobic resveratrol with its smaller molecular weight was mainly distributed in the dermis, whereas hydrophilic chlorogenic acid was found more in the epidermis [84].

In addition, the permeation of active substances through the skin depends also on the vehicle formulation. For example, lower oil contents in the emulsions often facilitate the release of phenolic substances as well as higher skin permeation rates [81, 85–88]. This behaviour can be contributed to a lower viscosity of low oil emulsions in contrast to emulsions with higher oil content. The higher viscosity of the latter ones might hinder the diffusion of phenolics within the emulsions. Hyperhydration of the skin by the application of formulations with high water contents could also be a reason for the higher skin permeability. The *Stratum Corneum* is relatively dry with a water content of about 20% under normal conditions; due to an increased hydration can occur the re-organization of lipid lamellar structures leading to an increased transdermal delivery of topically applied drugs [89].

Thermodynamically stable microemulsions can be also used as vehicles to enhance the skin permeation rates of polyphenols [84, 88, 90, 91]. The skin permeation of hydrophilic chlorogenic acid, formulated to O/W microemulsions, was enhanced in comparison with aqueous vehicles and W/O microemulsions (water-in-oil) [91]. The formulation of hydrophobic quercetin to a W/O-microemulsion, however, considerably improved the intradermal delivery; quercetin penetrated into deeper skin layers [88].

Some researchers associate enhanced permeation with the emulsifier used and suggest possible interaction of surfactant molecules with skin components. The incorporation of chlorogenic acid, resveratrol, curcumin and quercetin to O/W microemulsions, containing sucrose laurate or di-2-ethylhexyl sodium sulfosuccinate, could enhance the delivery of these polyphenols into the dermis *in vitro* in comparison with the microemulsions containing Tween 80 (polyoxyethylenesorbitan monooleate) [84, 90].

An improvement of skin penetration can be achieved using nanocarriers or nanoemulsions [92, 93]. For flavonones from *Eysenhardtia platycarpa* leaves, the enhancement of release and skin permeation rates and the improvement of anti-inflammatory activity due to the formulation of nanoemulsions and polymeric nanoparticles, respectively, were reported [93]. Comparing some nanocarriers with various composition, ethanol-containing vesicles based on soya phosphatidylcholine were shown to be most potent for the enhancement of skin permeation of resveratrol [92]. However, the blank vesicles, containing ethanol, exhibited cytotoxicity and led to an increase in ROS production. Nevertheless, the cytotoxic effect was not observed in vesicles, loaded with resveratrol; therefore, the authors suggest these formulations as topical agents with good skin delivery properties. However, a possible systemic effect of nanoformulations is not proven up to now; therefore, their use in the cosmetics is controversial and questionable.

An alternative way for penetrating active substances into the skin is the incorporation into the cosmeto-textiles. For example, incorporated resveratrol migrated into the skin layers *in vitro,* but more slowly as from the directly applied ethanolic vehicle; therefore, the cosmeto-textiles were proposed as a reservoir system for progressively delivery to the skin layers [94]. This delivery method is increasingly used in the cosmetics and pharmaceutical industries.

### *In vivo* effectiveness of polyphenols

As described above, numerous *in vitro* studies demonstrate a broad spectrum of positive properties of polyphenol extracts regarding possible prevention and therapy of skin diseases and improvement of skin condition. Moreover, the improvement of the formulation stability and the skin delivery properties of polyphenols have been studied intensively. However, there are only a few clinical studies which constrain the effectiveness of polyphenols and their 'anti-ageing' effect *in vivo*.

The photoprotective properties of polyphenols can be measured, when treated skin area is irradiated with UV light and the resulting erythema is appraised. A protective effect of topically applied EGCG against acute skin damage caused by UVA, ascertained in a rat study [95], or preventive action of chlorogenic acid against UV-induced erythema formation in the guinea pig skin [91], could be successfully confirmed for humans. Polyphenol extracts from pistachio nut significantly reduced UVB-induced skin erythema by topical application in human volunteers [15]; the extract from *E. angustifolium*, containing tannins, phenolic acids and flavonoids, also exhibited a photoprotective effect *in vivo* [43].

A protective effect of formulations containing green tea extract, against UV-induced photoageing and photoimmunosuppression, has been demonstrated in a study with 20 volunteers [96]. For example, the green tea extract was able to inhibit the expression of MMP-9 and MMP-2 which are particular responsible for the degradation of the extracellular matrix and consequently for photoageing and tumour generation.


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A study with 15 volunteers has shown that the topical treatment with resveratrol provided a protective effect against UV-induced sunburn and suntan. After repetitive UV radiation for consecutive 4 days, erythema on resveratrol-treated sites was barely seen and sunburn cell formation was significantly inhibited [97]. The combination of resveratrol, green tea polyphenols and caffeine could reduce facial redness. This effect was evaluated in a 12-week study with 16 volunteers [98].

More effort is required for the investigation of possible anti-ageing effects. These clinical trials should be double blind, placebo-controlled, randomized and conducted with within a longer time span with possibly large number of volunteers to achieve statistically relevant results. In these studies, a comparison before and after the treatment takes place; the biophysical parameters as skin roughness and wrinkling, elasticity and firmness, moisturization and skin density were the target responses [99]. Green tea extract is relatively well studied, but its effects on the skin are ambiguous. A clinical trial with 24 volunteers demonstrated a moisturizing effect of green tea extract as well as improving skin microrelief (reduction of roughness) and elasticity after 15–30 treatment days [100]. In another study, 40 women received green tea therapy as combination of topical treatment and oral supplementation or placebo within 8 weeks; the therapy resulted in a significant improvement of the content of elastic tissue, determined histologically, indicating an anti-ageing effect of the combined therapy. However, any clinically significant changes could not be observed [101]. Green tea extract, enriched in gallic acid, epigallocatechin and epicatechin due to tannase treatment, was shown to be more effective in the anti-wrinkle treatment than normal green tea extract [102].

The anti-ageing effect of some other polyphenolic extracts was evaluated in a 28-day clinical study. The formulation with ginkgo (*Ginkgo biloba* L.) extract increased skin moisturization and smoothness, reduced roughness and wrinkles. Efficient wrinkle reduction exhibited also the formula containing green tea (*C. sinensis* L.) and rooibos (*Aspalathus linearis* Burm.f.) [103]. A visible improvement of ageing signs as elasticity was achieved by the application of a cream containing transresveratrol, especially in the combination with beta-cyclodextrin as carrier, probably due to enhancement of the skin permeation rate [104].

Some clinical trials demonstrate that oral consumption of polyphenols can also improve skin conditions, leading for example to the diminishing of skin roughness, increased skin hydration and elasticity [38, 105–107]; a combined therapy (oral intake and topical application) seems therefore to be reasonable.

## Summary

The studies reviewed in this paper constrain that polyphenol-enriched extracts can be effective for the prevention and therapy of premature skin ageing, provoked by oxidative stress. This review comprises the beneficial properties of polyphenols, which are mostly relevant by the topical application, as antioxidant activity, protective action against UV damages, inhibition of dermal proteinases anti-microbial activity and anti-carcinogen action, which were determined *in vitro* using cell line assays. Some studies, however, reported about possible cytotoxic effects of polyphenols or about the possibility of reductive damages caused by polyphenols, which, in turn, were disproved by other researchers. The review of the present literature could not give a clear answer, if these supposed negative effects are really or not, but the majority of the scientific research is still related to the investigation of beneficial properties of polyphenols and of mechanism of their biological action. The formulations used for the topical application of polyphenol extracts are also intensively investigated and optimized regarding the skin delivery improvement. Some controlled clinical studies demonstrating the photoprotective or anti-ageing effects of topically applied or orally supplemented polyphenols. The number of these studies, however, is small; the most studies reported investigations with either green tea extract, or complex mixtures of several extracts and minerals, so that the data for the *in vivo* effectiveness of numerous extracts and products are not really available. Nevertheless, the beneficial effects *in vitro* as well as presented *in vivo* evidence demonstrate an enormous potential of polyphenolic extracts as active ingredients in topical applied products for the prevention and therapy of UV damages, skin ageing as well as cancer diseases.

## Acknowledgement

This work was financially supported by the Fraunhofer Gesellschaft zur Förderung der Angewandten Forschung e.V.

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