POLYPHENOLS APPLIED TO SKIN CARE

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Polyphenols are molecules found in plants. The beneficial properties of polyphenolic extracts, such as fulvic acid concentrates, demonstrate an enormous potential in topically applied products for the prevention and therapy of UV damage, skin ageing and cancerous conditions of the skin, as well as providing anti-microbial activity, and anti-carcinogenic properties.

In this article I have analyzed numerous studies on the benefits of plant compounds for skin care applications. Many of the studies are drawn from common plants you know, such as green tea or grapes. The fundamental active ingredient in these compounds are classified as polyphenols, which comprise antioxidants, organic acids, flavonoids and fulvic acids.

Both plants and humans have a photoprotective biochemical process that helps the cells cope with molecular damage caused by sunlight. Plants have developed a suite of photoprotective mechanisms to prevent oxidative stress caused by excessive or fluctuating light conditions.

Fulvic acid-bound minerals and organic acids, such as those in Mineral Logic's MLG-50™ are a complex of polyphenols containing flavonoids that supply antioxidants. The greater the supply of antioxidants, the more mitochondria the body produces, which strengthens its defense against free radical damage and DNA mutations throughout the body including the skin.

UF Irradiation and Oxidative Stress Explained

According to current knowledge, UV irradiation and oxidative stress are the main causes of extrinsic (premature) ageing of the skin[1-5]. UV radiation from the sun induces several harmful responses, including erythema (reddening of the skin, dilation of capillaries), immune-suppression, edema, sunburn, hyperplasia (increased cell replication), hyper-pigmentation, premature ageing and skin cancer.

Only UVA (320-400nm) and UVB (280-320 nm) are harmful to our skin. UVA accounts for more than 90% of the total UV radiation reaching us and is constant throughout the year, but UVB photons are one thousand times more capable of causing sunburn than UVA and increase considerably in the summer [6].

Oxidative stress is provoked by an excess of free radicals or reactive oxygen species (ROS), as a consequence of UV skin exposure. Under normal conditions, the natural endogenic antioxidant system of the skin (that is produced by the body) is very effective. It contains enzymes, such as glutathione peroxidase, glutathione reductase, catalase and superoxide dismutase, which degrade hydrogen peroxide, lipid hydroperoxides and superoxide – common free radicals.

Non-enzymatic antioxidants are, for example, the L-ascorbic acid in the aqueous phase in the skin, glutathione in the cellular compartment, α–tocopherol in membranes and ubiquinol in the mitochondria [4-5].

When our skin is exposed to oxidative stress, the effectiveness of the body's protective system is diminished. After irradiation of skin fibroblasts (collagen producing cells) with UVA, the activity of catalase and superoxide dismutase decreases [5]. ROS free radicals initiate chain reactions of lipid peroxidation in the cell membranes and disrupt the signal transduction pathways that are involved in the expression of genes, which in turn, regulate collagen metabolism [4-5].

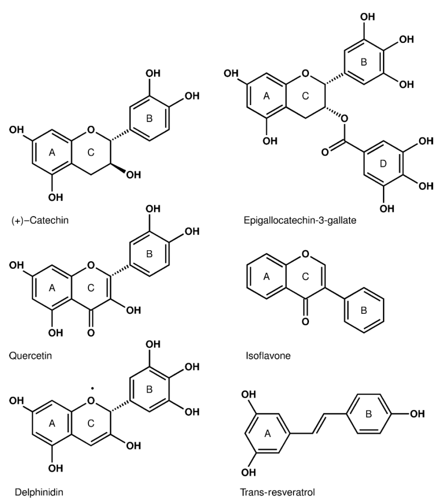

Figure 1 Representatives of flavanols (catechin, epigallocatechin gallate), flavones (quercetin), isoflavones (isoflavone), anthocyanidins (delphinidin), and stilbenes (trans-resveratrol).

For example, due to some signal cascades, an overexpression of matrix metalloproteinases (MMP) occurs. MMPs are a group of enzymes that include: MMP-1 (collagenase), MMP-3 (stromelysin) and MMP-9 (gelatinase). These enzymes accelerate the degradation of the corresponding proteins vital to the skin's integrity. The expression of MMPs occurs both in epidermal keratinocytes, and in dermal fibroblasts; therefore, these skin layers are particularly susceptible to sun damage [4-5].

Leading to DNA Damage
The genetic material is often damaged by UV irradiation as DNA can directly absorb UVB light. Exposure to UV facilitates mutations and errors in DNA replication. Furthermore, UVA can also inhibit DNA repair, invoking an additional stress on DNA integrity [5]. This effect and the described activation of MMPs and lipid oxidation increase the probability of cancer development and premature skin ageing.

Skin Care Support
To support the skin's endogenic antioxidant defense system, antioxidants, such as fulvic and phenolic acids, can be supplied either by the diet or applied directly to the skin. They can scavenge ROS and inactivate MMP enzymes that result in a normalized production of skin structural proteins [7]. Hence, preventive or reparative effects could be achieved in this way.

Structure of Polyphenols
The term 'polyphenols' includes a large group of molecular compounds, which all have more than one phenolic hydroxyl group, bound to one or more benzene ring systems (Figure 1). Flavonoids, also known as fulvic acids, are the main group of polyphenols. 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 is the source of 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 C-ring [8].

Sources of Polyphenols

The major sources of polyphenols are fruits and berries, vegetables, spices, oil seeds and tea [9]. Polyphenols are secondary plant metabolites, produced in minor amounts and not in the primary energy metabolism of plants; their functions in the plant are mainly the protection of the plant against UV radiation, pathogens and for the production of color in fruits and flowers.

Antioxidant Defense System

The skin possesses an elaborate antioxidant defense system to deal with UV-induced oxidative stress by utilizing antioxidants, vitamins and co-enzymes to protect and repair free radical damage within the layers of the skin. However, excessive and chronic exposure to UV radiation can overwhelm the cutaneous antioxidant capacity, leading to oxidative stress and oxidative damage, which may result in skin disorders, immunosuppression, premature ageing of the skin and development of melanoma and non-melanoma skin cancers.

Skin Care Products with Antioxidants

Topical application of antioxidative active substances can support the skin's own antioxidant system against oxidative stress and could protect the skin against photo-ageing over the long term. The antioxidant properties of polyphenols have been described extensively in the literature [8, 10] including those comprising the ingredients of MLG-50™ [11-22] that include gallic, caffeic, shikimic, fumaric, cinnamic, ferulic, benzoic, protocatechuic, phenylacetic, succinic, maleic, acetic, and lactic acids.

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, 23-25]. These methods reflect the potential protective action of polyphenol extracts on the skin against ROS damage, for example by UV irradiation.

Anti-collagenase and Anti-elastase Activity

Phenolic extracts are found to inhibit the activity of proteinases, which are enzymes that catalyze the degradation of healthy skin proteins, such as collagen and elastin. Collagen in the dermis is responsible for the firmness of the skin, elastin fibers lend the elasticity. Excessive free radical exposure provokes the expression of collagenase (MMP-1) and elastase, leading to the accelerated degradation of corresponding proteins and its associated skin damage.

Study: Thring et al. Determined anti-collagenase, anti-elastase and antioxidant activities of 21 plant extracts and correlated them with the total phenolic content. They demonstrated that white tea extract showed the highest inhibitory activity against both enzymes as well as the highest antioxidant activity and phenolic content [26].

Study: Lee et al. isolated a phenolic substance from Areca catechu L., (Areca palm) which effectively inhibited elastase and hyaluronidase – an enzyme, which catalyzes the degradation of hyaluronic acid in the extracellular matrix in the dermis – and supported its anti-ageing effect [27].

Study: 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 (cells in connective tissue which produces collagen and other fibers). **The most potent enzyme inhibitors, elucidated by this study, were the fulvic acids phloretin, 3-hydro phloretin, and quercetin**[28].

Protection Against UV Damage 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 a study performed by Nichols et al., were from 7 to 29, corresponding to 'minimal' (SPF from 2 to 12) and 'moderate' (SPF from 12 to 30) sun protection properties. This study supports that the rating of the polyphenol mixtures ranged from a 2-30 SPF activity in the absence of other sun blocking additives.

Moreover, the possibility of preventing or reducing UV-induced photodamages makes polyphenols relevant to topical ingredients. In a recent review, the photoprotection properties of polyphenols have been summarized in Table 1 [29].

A number of studies describe the effects of polyphenolic extracts on human cells and UV-irradiated cells. The pre-treatment of HaCaT keratinocytes (human skin cell-line) with polyphenols or phenolic extracts leads to a decreased intracellular ROS (free radical) formation, induced by UVB or hydrogen peroxide.

Study: In addition, the prevention of DNA damage, attenuated DNA pyrimidine dimer formation, and prevention of cell apoptosis (cell death) was observed [25, 30, 31]. The treatment of normal human dermal fibroblasts (NHDF) with *Epilobium angustifolium* (a flowering plant named Fireweed) 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 hyaluronidase 2; and the viability of the NHDF cells were also improved due to the extract treatment [32].

Study: Strawberry extract, containing mainly flavonoids and anthocyanins, protected dermal fibroblasts from oxidative stress induced by hydrogen peroxide (H_2O_2). Pre-incubation with the strawberry extract resulted in an increased cell viability, decreased intracellular amount of ROS, a reduction of membrane lipid peroxidation and DNA damage [33].

Study: Potapovich et al. demonstrated that the post-treatment of normal human epidermal keratinocites (NHEKs) after UV exposure with polyphenols (resveratrol, quercetin, verbascoside) was effective to abolish the overproduction of peroxides and inflammatory mediators [34].

Studies on the Effect of Polyphenols on the Cell Viability

The numerous positive effects of polyphenols described above lead to their increased use as cosmetic ingredients or food additives. The polyphenol-rich strawberry extract, investigated by Giampieri et al., demonstrated protection of human dermal fibroblasts against hydrogen peroxide oxidative damage and improved mitochondrial functionality [33].

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]

Study: Negrao et al. studied the effects of catechin on angiogenic and inflammatory processes. Treatment with catechin, a natural phenol and antioxidant, increased viability, decreased apoptosis or cell death and inflammation of endothelial cells and vascular smooth muscle cells *in vitro* [35].

Study: Chamcheu et al. demonstrated that delphinidin, a plant anthocyanidin and antioxidant, significantly enhanced keratinocyte differentiation of NHEKs – these are stem cells that reside in the basal layer of the epidermis. These cells divide to give rise to the transient amplifying cells which divide further and differentiate as they move up in the epidermis [36].

Cosmetic Application of Polyphenols

The beneficial effects of polyphenols as functional ingredients have attracted considerable attention from the pharmaceutical and cosmetic industries in recent years. As a consequence, many skin care products or 'cosmeceuticals' have been developed based on polyphenol-enriched extracts. To exert their designated biological activities, topically applied substances need to be released from the formulation to reach the skin and finally to overcome the *Stratum Corneum* – the horny outer layer of the skin – barrier and penetrate into the epidermis and dermis. The release of active substances and further skin permeation depends on the molecular properties such as molecular weight and lipophilicity, but also on the vehicle (oil based, water based) formulation [37,38].

The formulations must be chemically, physically, and microbiologically stable to assure the stability and deliverability of active substances to the target skin layers.

The fulvic acids in MLG-50™ are derived from a natural source deposit in the United States. Through a clean extraction by purified water and concentrated product is produced that is stable in a wide pH range. Fulvic acids are both hydrophilic (water-loving) and lipophilic (fat-loving0 making them ideal for skin care products to aid in hydration and to remain homogenized in skin care formulations.

Effectiveness of Polyphenols Studies In vitro

Numerous *in vitro* studies demonstrate a broad spectrum of beneficial properties of polyphenol extracts regarding possible prevention and therapy of skin diseases and improvement of skin condition. Moreover, improvement of formulation stability and skin delivery properties of polyphenols have been studied intensively. Clinical studies have been performed that support the effectiveness of polyphenols, their 'anti-ageing' effect, and beneficial effects of polyphenols protective effect against exposure to UV, photo-ageing and photo-immunosuppression.

Study: Polyphenol extracts from pistachio nut significantly reduced UVB-induced skin erythema by topical application in human volunteers [39]. The extract from *E. angustifolium* (cottongrass) containing tannins, phenolic acids and flavonoids, also exhibited a photoprotective effect *in vivo* [32].

Study: A protective effect of formulations containing green tea extract, against UV-induced photo-ageing and photo-immunosuppression, has been demonstrated in a study with 20 volunteers [40]. For example, the green tea extract was able to inhibit the expression of MMP-9 and MMP-2 which are responsible for the degradation of the extracellular matrix and consequently for photo-ageing and tumor generation.

Study: A study with 15 volunteers demonstrated that topical treatment with resveratrol provided a protective effect against UV-induced sunburn and suntan. After repetitive UV radiation for a consecutive 4 days, erythema (reddening of the skin) on resveratrol-treated sites was barely noticeable and sunburn cell formation was significantly inhibited [41].

Study: In another study, the combination of resveratrol, green tea polyphenols and caffeine reduced facial redness. This effect was evaluation in a 12-week study with 16 volunteers [42]. In these studies a comparison before and after the treatment was performed. The biophysical parameters of skin roughness and wrinkling, elasticity and firmness, moisturization and skin density had significantly improved, as a result of topical treatment containing polyphenols [43].

Study: Green tea extract applied topically is relatively well studied. 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 days of treatment [44]. In another study, 40 women received green tea therapy consisting of a combination of topical treatment and oral supplementation or placebo over an 8 week period; the therapy resulted in a significant improvement of elastic tissue, determined histologically, indicating and anti-ageing effect of the combined therapy [45].

Study: Green tea extract, enriched with gallic acid, epigallocatechin and epicatechin, was shown to be more effective in anti-wrinkle treatment as compared to that of the unenriched green tea extract [46].

Study: The anti-ageing effect of various polyphenolic extracts was evaluated in 28-day clinical studies. A formulation with ginko (*Ginko biloba L.)* extract increased skin moisturization, smoothness and reduced roughness and wrinkles.

Study: In another study efficient wrinkle reduction was exhibited utilizing the formula containing green tea (*C. sinesis L.)* and rooibos (*Aspalathus linearis* BURM.F.) [47].

Study: Lastly, a visible improvement of ageing signs such as elasticity was achieved by the application of a cream containing trans resveratrol – the isolated active ingredient in resveratrol – especially in the combination with beta-cyclodextrin as the vehicle carrier, probably due to enhancement of the skin permeation rate [48].

Conclusion Summary:
These studies suggest that polyphenolic extracts are very useful ingredients for both sunscreens – as preventative – and after-sun – as therapeutic – cosmetic products. As photodamage can lead to the formation of skin cancer, the properties described above suggest the positive effects of polyphenols during anti-cancer therapy. Polyphenols have anti-carcinogenic effects as demonstrated in several skin tumor models [52,53]. They also support the skin's clarity, elasticity, smoothness, hydration and firmness.

We see clearly from the above clinical studies done both in the laboratory (*in vitro)* and in clinical human trials (*in vivo)*, that the antioxidant properties of polyphenols have been described extensively in the literature [8,10] including those comprising the ingredients of MLG-50™ [11-22], which include gallic, caffeic, shikimic, fumaric, cinnamic, ferulic, benzoic, protocatechuic, phenylacetic, succinic, maleic, acetic, and lactic acids.

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