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# The inhibitory effects of polyphenols on skin UV immunosuppression*

## Wpływ związków polifenolowych na zahamowanie immunosupresyjnego działania promieniowania UV na skórę

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## Summary

Long-term exposure to UV radiation leads to skin ageing and may initiate carcinogenesis. In both cases immunosuppressive activity of UV radiation plays an important role. The aim of the study is to present polyphenols commonly seen in flora and their properties protecting the skin from the damaging influence of UV rays. Polyphenols are a group of compounds which are present in plants. Their common features are: the ring structure of a molecule, hydroxyl groups in the rings and a conjugated double bond system. Such structure makes polyphenols active antioxidants. They also demonstrate anti-immunosuppressive properties.

**Keywords:** **UV • skin • polyphenols • antioxidants • anti-immunosuppression • polyphenols • UV radiation • flavonoids • phenolic acids • immunosuppression**

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Long-term exposure to UV radiation leads to skin ageing and may initiate carcinogenesis. In both cases immunosuppressive activity of UV radiation plays an important role [4,12,13,29].

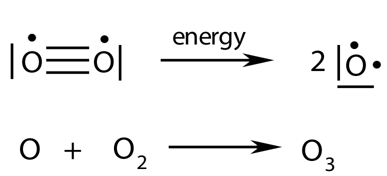
In physiological conditions, in cell mitochondria, a process of oxidative phosphorylation takes place. As a consequence, a certain number of reactive oxygen species (ROS) appear. They are deactivated by mechanisms of antioxidative barrier. UV radiation considerably enhances generation of ROS. They, in turn, increase secretion of the cytokine interleukin 10 (IL-10), which is characterized by strong immunosuppressive activity [2,23,29].

ROS can also damage tissues and DNA structure as well as enhancing migration of Langerhans cells from the epidermis to the dermis and then to surrounding lymph nodes. It contributes to a decrease in the number of Langerhans cells in the epidermis, which leads to local immunosuppression. That condition may be directly connected with skin carcinogenesis [3,6,13,24,25].

In order to prevent any potential UV radiation-induced changes, the skin develops self-repair mechanisms, i.e. pigmentation and absorption of UV radiation by melanocytes or removal of damaged fragments of DNA by particular enzymes. Applying sun protection filters, absorbing or reflecting UV radiation, is not usually sufficient protection against UVA radiation, which also contributes to the development of free radicals as it penetrates to deeper layers of the skin than UVB radiation [13,14].

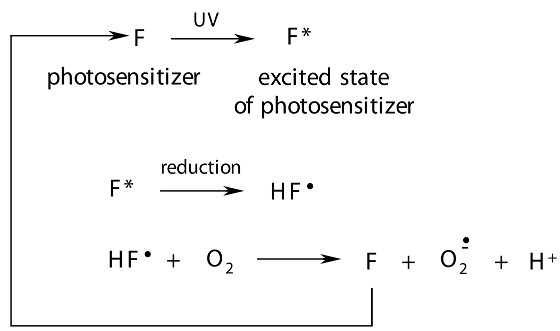
Therefore, scientists are constantly trying to create new, more effective compounds which can be administered not only topically but also systemically. The aim of the study is to present polyphenols commonly seen in flora and their properties protecting the skin from the harmful influence of UV rays.

Absorption of UV radiation by skin chromophores leads to excitation, ionization and disintegration of cells and development of free radicals. UV radiation also contributes to breaking down of oxygen molecules (a radical which has paramagnetic properties) into atomic oxygen, which having reacted with other oxygen molecules turns into a molecule of ozone, $O_3$. It is a substrate in reactions which result in forming ROS such as singlet oxygen, but it also is a strong oxidant [30].




Some chemical compounds, called photosensitizers, can intensify ROS generation. Such structures are capable of absorbing ultraviolet radiation, which leads to the occurrence of adverse skin reactions (phototoxic and photoallergic reactions). Both cell metabolites (endogenous photosensitizers) and substances which are externally applied (exogenous photosensitizers) can serve as photosensitizers. Substances from the other group can be found in some herbs (e.g. in St. John's wort (*Hypericum*)), cosmetics (e.g. perfumes) and drugs (e.g. hormonal).

A highly reactive and excited state of the photosensitizer molecule can undergo single-electron reduction. The reduced photosensitizer molecule reacts with an oxygen molecule, becomes oxidized and forms a superoxide anion radical. The superoxide anion radical, in the course of further modifications, might be a source of other reactive oxygen species.




The excited photosensitizer molecule in a triplet state (with unpaired electrons) can react with oxygen whose basic state is also a triplet state. As a result of this reaction two molecules in a singlet state, including singlet oxygen, are formed.

$$^{1}F \xrightarrow{UV} {}^{3}F^{*}$$

$$^{3}F^{*} + {}^{3}O_2 \longrightarrow {}^{1}F + {}^{1}O_2$$

Usually, during the exposure to UV radiation, ozone, a superoxide anion radical and singlet oxygen appear simultaneously [22].

Polyphenols are a group of compounds which are present in plants. Their common features are: the ring structure of a molecule, hydroxyl groups in the rings and a conjugated double bond system. Such structure makes polyphenols active antioxidants. The compounds easily become oxidized and they turn into quinones. Intermediate forms are highly reactive phenoxyl radicals, stabilized by delocalization of unpaired electrons in the aromatic ring [8,21].

Natural polyphenols are substances which are characterized by reducing properties. These properties protect lipids in intracellular cements from oxidation and positively influence collagen synthesis [21]. They also bind free radicals, starting with, among others, hydroxyl radicals and superoxide anion radicals and finishing with lipid radicals. They can stabilize or delocalize an unpaired electron or modify ROS into less reactive systems, by hydrogenating or complexing them. These substances often serve as agents chelating metal ions of enzymes catalyzing oxidation reactions, oxidase inhibitors or terminants breaking radical chain reactions. In the dermis the substances influence the condition of blood vessels and stimulate skin microcirculation. They are natural filters protecting against solar rays, especially UVA rays, which damage the dermis [19,21].

Polyphenols, including phenolic acid (benzoic and cinnamic acid) derivatives and flavonoids, demonstrate antioxidative properties.

Ferulic and caffeic acids as well as their derivatives make up the most important phenolic acids which act as antioxidants. They are compounds whose structure is composed of an aromatic ring and hydroxyl and carboxyl groups. A different level of antioxidative activity of phenolic acids results from their chemical structure and depends on the number and position of hydroxyl groups. The presented properties are enhanced if esterification of particular hydroxyl groups takes place. Caffeic acid, which is a dihydroxy acid, demonstrates antioxidative properties that are comparable to those of monohydroxy ferulic acid. The activity of the latter is enhanced by an electron-donating (methoxy) group in the *ortho* position in comparison to a hydroxyl group.

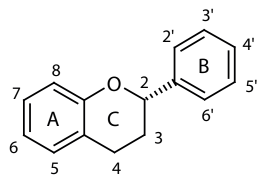
The presented phenolic acids are often called inhibitors of neoplastic diseases. Great amounts of these substances can be found in many plants, e.g. coneflower (*Echinacea*) or *Polypodium leucotomos.* They efficiently bind radical oxygen, and neutralize superoxide anion radical, hydroxyl radical and singlet oxygen which are induced by UV radiation. In that way they inhibit the course of free radical reaction, prevent the process of skin ageing and development of neoplasms [5,15,16,28].

ROS contribute to intermolecular cross-link formation of collagen III. It loses its water solubility and elasticity. The skin loses its firmness, which results in the formation of wrinkles. Phenolic acids protect collagen against degradation by accelerating regeneration of cells. They are therefore used as agents against photodamage of the skin induced by UVA and UVB radiation.

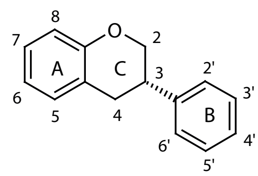
Moreover, ferulic and caffeic acids inhibit glutathione (GSH) oxidation and generation of its oxidized form, glutathione disulfide (GSSG), which forms in the reaction of GSH and hydrogen peroxide. Thanks to that it is possible to maintain quantitative balance between these substances in the body. Glutathione disulfide is a dangerous substance for a cell as it might lead to protein deactivation. The thiol group of GSH readily reacts with free radicals of organic substances, which leads to the repair of damaged molecules and formation of a free radical of glutathione. The main function of GSH is to maintain a reduced number of protein thiol groups and maintain functional activity of these structures [16,17].

Additionally, phenolic acids prevent Langerhans cells from migrating from the epidermis to neighbouring lymph nodes, and thus they provide an immunoprotective effect. They also prevent morphological changes to Langerhans cells, such as the loss of dendritic processes or granular atrophy [1,16,26].

Another polyphenol group which is characterized by highly antioxidative properties, and therefore anti-immunosuppressive ones, is the flavonoids. Their molecule consists of two benzene rings (A and B), between which there is a heterocyclic ring of pyran or pyrone (C).




FLAVONOIDS




ISOFLAVONOIDS

In molecules of the majority of natural flavonoids ring A contains two hydroxyl groups at positions 5 and 7 and ring B contains a hydroxyl group at position 3 (catechol group). In a flavonoid molecule at the carbon atom at position 2 of the heterocyclic ring there is usually a hydroxyl group or phenyl substituent. In isoflavonoids they are located at the carbon atom at position 3.

The level of antioxidative activity of flavonoids depends on the number and location of hydroxyl groups. A large number of hydroxyl groups may enhance that activity. Two OH groups in ring B in the *ortho* position and one hydroxyl group at position 5' appear to be of high importance. Hydroxylation of benzene rings at positions 5 and 7 might decrease the antioxidative properties of flavonoid.

A methoxy group in a flavonoid molecule, because of its size and blocking a hydroxyl group, decreases antioxidative properties of the compound. Some findings indicate that methylation of the hydroxyl group of C7 carbon atom in isoflavonoids does not reduce the ability to inhibit the peroxidation process.

In plants flavonoids take the form of saccharides. A saccharide residue is usually bound to the carbon atom at position 3 or 7. Owing to the blockage of hydroxyl groups by the sugar residue, glycosides show weaker antioxidative properties in comparison to corresponding aglycones. Differences in antioxidative properties also depend on the kind of saccharide residue present in the molecule.

Glycosidation of the hydroxyl group at the carbon atom at position 3 of the monosaccharide molecule does not reduce the antioxidative capability of flavonoids; antioxidative activity is significantly lower than in the case of glycosidation with a disaccharide residue.

Antioxidative activity of flavonoids includes the inhibition of enzymes responsible for producing superoxide anion radicals (such as xanthine oxidase, protein kinase C), decrease in the activity needed to generate the superoxide anion radical of membrane NADPH oxidase, chelating transition metals, "scavenging" free radicals and stimulation and protection of other antioxidative factors.

Flavonoids not only inhibit the generation of ROS but also deactivate already existing oxygen radicals. Because of their low redox potential flavonoids are thermodynamically capable of reducing most free radicals by donating a proton:

$$Fl-OH+R\cdot\rightarrow Fl-O\cdot+RH$$

The radical which comes from a flavonoid molecule (FL-O·) reacts with another similar radical and forms a quinone structure. Superoxide anion radical, singlet oxygen, hydroxyl radical and lipid radicals are the easiest to capture. Neutralizing superoxide anion radical and singlet oxygen leads to turning flavonoids into stable products. Capture of other radicals results in the formation of unstable products which undergo further radical reactions. Reaction of flavonoids with a hydroxyl radical, readily reacting with aromatic compounds, is particularly effective. Catechins, which constitute one group of flavonoid compounds, demonstrate an ability to capture hydrogen peroxide and superoxide anion radical.

Iron and copper ions enhance the development of ROS by the reduction of hydrogen peroxide and generation of hydroxyl radicals or by catalyzing oxidation of low-density lipoproteins (LDL).

$$H_2O_2+Fe^{2+}(Cu^{+})\rightarrow\cdot OH+OH^{-}+Fe^{3+}(Cu^{2+})$$

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By chelating transition metals ions, including iron and copper ions, flavonoids play an important role in oxygen metabolism [7].

Various kinds of flavonoids, which act as photoprotective antioxidants, can be found in many plant extracts. These substances prevent, or at least reduce, negative effects of UVA and UVB radiation, including damage to DNA (e.g. fragmentation) and mtDNA structure. They also reduce the development of pyrimidine dimers, keratinocyte apoptosis or gene mutations. They do not allow UV radiation to initiate isomerization of urocanic acid. Urocanic acid is an endogenous substance, a histidine derivative, which in the horny layer of the epidermis appears in a slightly soluble *trans* form and in that form is a main component that absorbs UV radiation. After absorption the component undergoes isomerization, which results in the formation of a readily soluble *cis* form. This form acts immunosuppressively and inhibits the antigen presentation process by Langerhans cells. The *cis* isomer does not only act topically. It is also spread throughout the body and it leads to systemic immunosuppression by reducing the number of T lymphocytes and making the processes connected with antigen presentation less intensive. Such processes may lead to increased exposure to infections and carcinogenesis. On the other hand, the *cis* form influences epithelial cells of blood vessels and reduces TNF-α secretion, which has a direct effect on Langerhans cells. TNF-α is a factor attracting Langerhans cells. Decrease of the amount of this factor leads to a decrease in the number of Langerhans cells and weakening of processes of antigen presentation. It was scientifically proved that long-term exposure to UVB radiation results in thymus atrophy and thus systemic immunosuppression [13,20,23].

Application of cosmetic products having extracts of green tea (*Camellia sinensis*), which contain flavonoids from a catechin group, leads to a decrease in the number of signs of ageing. It was proved that 3% extract from green tea is sufficient protection against photoageing and photoimmunosuppression, owing to the fact that it prevents the reduction of the number of Langerhans cells in the epidermis [9,10,13,18,27,29,31].

Another interesting flavonoid is silymarin, found in milk thistle (*Silybum marianum*). It contains the isomers silybin, isosilybin, dihydrosilybin, silydianin and silychristin. These compounds have been proven to inhibit photocarcinogenesis by a decrease in oxidative stress and "repair" the damage to DNA induced by UV radiation. If such repair is possible, silymarin prevents apoptosis of keratinocytes and fibroblasts which contain the damaged fragment of DNA. The number of pyrimidine dimers is reduced, too. The dimers are molecules formed as a consequence of DNA damage. They exert an immunosuppressive effect and even a carcinogenic effect [11,18].

Researchers constantly attempt to counteract the harmful effects of UV radiation. The methods implemented so far do not fully protect the skin against antioxidative and immunosuppressive processes. Sun protection filters do not appear to be entirely effective. Other findings indicate that even preparations with a maximum sun protection factor (SPF) will not help to avoid carcinogenesis. Bearing all this in mind, researchers are constantly seeking plants that contain compounds from polyphenol groups and that demonstrate antioxidative and anti-immunosuppressive properties. There are also attempts to find some ways of relieving signs of ageing.

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