FLAVONOIDS: A REVIEW FOR COSMETIC APPLICATION. PART TWO

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Summary

Flavonoids are now recognised as essential dietary components, although their functions are just on the brink of understanding. Dietary requirements have been established. Their significance is probably equal to vitamins. Approximately 5000 flavonoids have been identified, and the list is quickly expanding. The functionality of flavonoids is frequently “multi-purpose”, contrary to vitamins, enzymes and (to a lesser extent) hormones.

Riassunto

I flavonoidi sono riconosciuti come componenti essenziali delle diete, anche se non sono state ancora comprese appieno le loro funzioni. Comunque ne è stato riconosciuto il loro ruolo dietetico che dovrebbe essere simile a quello delle vitamine.
Circa 5000 sono i flavonoidi già identificati ed il loro numero si incrementa di continuo. Al contrario delle vitamine, degli enzimi e degli ormoni, l’attività di questi composti naturali è più complessa e serve a molteplici scopi.
BIOSYNTHESIS OF FLAVONOIDS

Robinson (8) suggested that the C15-skeleton of flavonoids is composed of two parts: a phenolic compound with six carbon atoms and an alkyl substituted phenolic compound with nine carbon atoms. The total biosynthesis is not yet known, but it has been shown, that the phenolic compound with six carbon atoms is constructed from acetic acid using acetyl-coenzyme A. This was concluded from feeding red cabbage plants with C-labelled acetic acid. Several authors also suggest that malonyl-coenzyme A is involved in this process. Virtually all reaction sequences in the biosynthesis of flavonoids are enzyme controlled. Typical phenolics are catechol, quinol and resorcinol.

The alkyl substituted phenolic compound follows the shikimic acid (3,4,5-trihydroxycyclohexene-1-carboxylic acid) pathway. This results in the formation of (substituted) cinnamic acid. This has been concluded from experiments using C-labelled shikimic acid, phenylalanine and 4-hydroxycinnamic acid, which all showed to be precursors for quercetin. It has become evident, that especially phenylalanine plays a determining role in the biosynthesis of flavonoids.

THE FUNCTIONALITY OF FLAVONOIDS

Relative to the functionality of flavonoids most attention has probably been given to their ability to act as powerful anti-oxidants. The US Department of Agriculture have done and delegated a wide variety of studies relative to the anti-oxidant properties of flavonoids and has defined the so-called Oxygen Radical Absorbance Capacity (ORAC). Among fruits prunes are the absolute leaders when it comes to ORAC value, while red grapes, blueberries and raspberries are excellent followers. In the range of vegetables spinach, Brussels sprouts, alfalfa and broccoli score high. A recent study showed that a high ORAC diet raised the antioxidant capacity of the blood in the range of 10-25%.

Table XI and XII give some ORAC data of particular flavonoids.

<table>
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<td>ORAC values expressed as concentration (in μMole) whereby 50% inhibition of lipid peroxidation occurs.</td>
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<tr>
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<tr>
<td>Baicalein</td>
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<td>Quercetin</td>
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<td>Myricetin</td>
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<td>Baicalin</td>
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<td>Hyperoside</td>
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Also the antioxidant qualities of green tea flavonoids can clearly be demonstrated using the ORAC values (9, 10).

The ORAC values of antioxidants are not only significant for food additives but also for personal care and cosmetics. Skin ageing is usually related to lipid peroxidation and thus oxidation of the bio-membranes present in the sub-cutaneous tissue. Also oxidative stress, oxidation of squalene to squalene hydroperoxide instead of squalene-2,3-epoxide (which is the precursor for steroid hormones) is a significant ageing factor. The efficacy of flavonoids as anti-oxidants is related to their ability to quench oxygen-based free radicals, such as singulet oxygen, HO2· and
Free radicals are often brought into connection with the occurrence of skin defects and premature skin ageing, particularly in conjunction with over-exposure to UV-A and UV-B radiation (photo-ageing; dermatohelirosis). In cosmetic practice it is common practice to compensate these effects using vitamin C and/or vitamin E. Topical application of flavonoids such as quercetin and rutin (the glycoside of quercetin with rutinose; rutinose is the disaccharide of glucose and mannose) has been shown to be at least 60 times more active than ascorbic acid (vitamin C) and 350 times more than tocopherol (vitamin E). In actual fact, tocopherol is only a weak anti-oxidant.

It was also found that many flavonoids are able to protect human dermal fibroblasts significantly better than vitamin C/E, irrespective the stability of especially vitamin C: ORAC values of ascorbic acid and d-α-tocopherol are in the mMole range. In addition, flavonoids are also able to protect products vulnerable to oxidation, such as ascorbic acid and tocopherol, and it is therefore not surprising that e.g. the combination {vitamin C+rutine} is much more effective than the individual ingredients. After all, vitamin C is an important co-factor for various enzymes; skin lightning is a beautiful exponent thereof.

The protective effect of flavonoids obtained from bilberries and grapes has been demonstrated by Monboisse et al. (11). Calf skin acid-soluble collagen was exposed to free oxygen radicals produced by xanthine oxidase/hypoxanthine. Determination of the level of 4-hydroxyproline was monitored and it was shown that the collagen degradation could be completely inhibited with these flavonoids.

Many flavonoids exhibit anti-allergic properties and some are claimed for their anti-viral properties (12). Hesperidin, rutin, quercetin, quercitrin and aurantin were examined against vesicular stomatitis virus (VSV) action on mouse fibroblasts and hesperidin was also tested against influenza virus. Protection could be achieved for a period of 24 hours for a one-dose application of 200 µg/ml flavonoid. The results are preventive rather than curative, but this application seems to be most suitable indeed for skin care products for the inhibition of topically active viruses such as the herpes simplex virus. It goes without saying that cosmetic products, especially facial care, are usually prophylactic rather than reparative.

Also a large number of references have been made to the anti-inflammatory, anti-thrombotic, diuretic, fungicide and bactericide activity of flavonoids. Significant is also the stimulating effect to protein synthesis. Many of these properties boil down to the ability of flavonoids to interact with all kinds of enzymes.

A number of flavonoids have been demonstrated to be co-factors for enzymes. In this terminology they could be considered comparable to vitamins.

| Table XII |
| ORAC values of some green tea flavonoids |
| (-)-(2R,3R-Epicatecin Gallate | 10,0 |
| (-)-(2R,3R-Epigallocatecin Gallate | 11,0 |
| (-)-(2R,3R-Epigallocatecin | 16,0 |
| (-)-(2R,3R-Epicatecin | 30,0 |
Although in many cases only a limited selectivity of flavonoids for particular enzymes is observed, an increasing number of publications appear in the scientific literature reporting about an unexpectedly high degree of selectivity for particular enzymes.

It has been shown that many flavonoids are able to strengthen the fragile capillary blood vessels, and thus are an excellent tool to fight couperosis. Frequently the damaged blood vessels, particularly around the nose and on the cheeks will negatively influence the facial appreciation. Ginkgo biloba is a well-known source for flavonoids, and this extract is a very potent product to treat couperosis. This effect has also been observed using rutin when mice were exposed to excessive X-raying, which results in destruction of the arteries (Bruckner). The rate of survival increased from 31% to 56%. For that reason rutin is used for treating radiation sickness in men, e.g. the victims of radiation accidents in nuclear installations and it is also clinically applied for patients that suffer from erythraemia due to γ-irradiation.

A greatly less examined source of flavonoids for use in personal care and cosmetics are extracts of different nuts such as bitter almond (Prunus amygdalus), plums (Prunus domestica, containing the flavonoid prunetol) and black cherry (Prunus serotina). These extracts are very potent inhibitors for a number of enzymes. It is also interesting to note that the fatty acid composition of black cherry oil (also named wild cherry oil) and prune oil is fully in line with the chemical properties of the flavonoids as they occur in the fruit flesh.

The extract of peach (Prunus persica) and apricot (Prunus armeniaca) contain the flavonoid prunasin that inhibits the conversion of dopachrome to melanin, and for obvious reasons these extracts have been proposed and patented for skin whitening.

Flowering peach (Prunus davidiana) is already known for 3000 years to lower glucose levels in the blood of diabetes type II patients. It certainly is a functional remedy to treat type II diabetes patients, but this property also could be applied for slimming products. The active substances have been determined as flavonoids: catechin, prunin (naringenin-7-O-glucoside) and hesperidin-5-O-glucoside. Also myriceline and dihydromyriceline have been proposed for that application.

In addition to the anti-oxidant activity the physiological effects of many flavonoids can be explained as a distinct influencing of the enzyme system of the organism. Application can be done orally or topically. Given the fact that many flavonoids are water-soluble, transdermal application is certainly a valid mechanism, and probably better controllable than oral or intravenous application. However, many flavonoids are poorly soluble and will precipitate/crystallise at room temperature. In that case excellent results have been obtained by incorporation of flavonoids such as quercetin and/or rutin in the liquid crystalline matrix of suitable emulsifiers. The flavonoids are mono-molecularly soluble in the liquid crystalline matrix and the bio-availability is therefore significantly higher compared to a system that does not utilise a liquid crystalline matrix. It has also been demonstrated that the activity of poorly soluble flavonoids can be improved when applied in unsaturated phosphatidyl choline organogels.

Rutin (and to a lesser extent esculetin) are well-known inhibitors for the enzymes aldose reductase, lipoxygenase and phosphodiesterase. It dramatically strengthens the capillaries, has bactericidal and antiviral properties, and a variety of properties that are pharmaceutical by nature. Rutin is also highly appreciated for its ability to avoid erythraemia. This is beneficially applied in sun care products, having said that rutin is not classified as a UV filter.

The 3-rhamnoside of the flavonoid quercetin is named quercitrin. Quercetin and quercitrin occur in apples, all kinds of berries, onions (in The
Netherlands 54% of the oral flavonoid intake comes from onions, and 28% from apples), but also in nuts, flowers and the bark of many trees to which it gives a typical yellow colour.

Quercetin also occurs in significant amounts in botanical extracts such as Ginkgo biloba (ginkgo), Hypericum perforatum (St. John's wort), Sambucus canadensis and Sambucus nigra (elder). Quercetin and quercitrin are potent antioxidants and have a strong interaction with enzymes. Quercetin inhibits xanthine oxidase and in vitro experiments have shown that it also inhibits lipid peroxidation. This is most significant indeed as peroxidation of the unsaturated fatty acids in the subcutaneous membranes results in premature ageing.

Anti-inflammatory properties of quercetin and quercitrin appears to be due to its anti-oxidant and inhibitory effects on inflammation inducing enzymes such as cyclo-oxygenase and lipoxygenase, and the subsequent inhibited formation of leukotrienes and prostaglandins. There is also evidence that quercetin and quercitrin inhibit elastase, collagenase, hyaluronidase and tyrosinase. All these enzymes are most significant to the cosmetic chemist as they enable to control and manipulate the quality of the skin. No data on adverse effects of excessive dosage of flavonoids have been reported. The effective concentration of flavonoids such as quercetin, quercitrin and rutin in cosmetic preparations is low (0.05-0.15%), although also at this low concentration the solubility of these flavonoids may be a limiting factor in formulation development.

Noteworthy is the normalising effect of flavonoids on the enzyme system. Many processes that result in skin disorders boil down to a disturbed enzyme balance on the skin and in the subcutaneous tissue. Flavonoids are a fabulous and safe tool to alleviate these disorders. Although many botanical extracts are also a significant source for flavonoids, their concentration is usually significantly lower and to reach a similar level of bio-activity a high concentration of botanical extract is required, to such an extent that also side effects of undesired products may become apparent.

**BOTANICAL EXTRACTS RICH IN FLAVONOIDS**

Botanical extracts are often rich in flavonoids, and the diversity can be massive. In many publications first priority is given to the antioxidant properties of these flavonoids, but it has become clear that flavonoids have a far more significant role in topically applied products. Many flavonoids act as co-factors for all kinds of enzymes. As an example 3-galloyl-3',4',5,5',7-pentahydroxyflavanone (EGCG), a flavonoid that occurs in camellia sinensis (green tea), has been demonstrated to inhibit the enzyme squalene monooxygenase. This reaction is important for the conversion of squalene to lanosterol/cholesterol (13).

Enzyme manipulation via flavonoids is probably a general working mechanism in the human body by adjustment of the dietary habits, but also on the surface of the body via personal care and cosmetic products. The total amount of flavonoids acquired via the daily food intake has been shown to be insufficient because of improper dietary habits. Consequently the amount of flavonoids topically present is in general insufficient to allow the topical enzyme system to perform smoothly. A similar discussion continuously takes place on vitamins (also important, indispensible, cofactors for enzymes).

**Chamomile (Chamomilla recutita)**

Three well-known species of chamomile are in use: German or wild chamomile (Chamomilla recutita), Roman chamomile (Anthemis nobilis) and golden chamomile (Anthemis tinctoria). Roman chamomile is commercially cultivated. Chamomile is an extremely rich source of flavo-
noids: apigenin, luteolin, quercetin, apiin,isorhamnetin, patuletin, and a wide variety of glycosides such as apigenin-7-acetylglucoside, luteolin-7-glucoside, luteolin-4'-glucoside, luteolin-7-rutin-loside, 6-hydroxy-luteolin-7-glucoside, quercetrin, patulitrin, rutin, hyperoside, isorhamnetin-7-glucoside and chrysoeriol-7-glucoside. Also a number of coumarins are present, specifically to be mentioned coumarin, umbelliferone, methylumbelliferone and herniarin.

Luteolin, as it occurs in chamomile, is a highly useful substance; reported activities: aldose-reductase inhibitor, antiangiogenic, anticarcinogenic, antioestrogenic, antimutagenic, antimutagenic, antitumour (powerful), no-synthase inhibitor, metalloproteinase inhibitor, succinoxidase inhibitor, xanthine oxidase inhibitor, topoisomerase inhibitor.

Chamomile extract has anti-inflammatory, anti-itching, antiseptic, bactericidal and disinfectant properties. The beneficial properties of chamomile extract are well documented, and many properties of the chamomile extract that product development chemists use boil down to enzyme manipulation using flavonoids present in the extract.

**Amaranth (Amaranthus caudatus)**

In foods, amaranth is used similarly to wheat as a cereal grain. It was one of the staple foodstuffs of the Incas, and it is known as kiwicha in the Andes today. It was also used by the ancient Aztecs, who called it huautli. Amaranth species are cultivated and consumed as a leaf vegetable in many parts of the world. In Indonesia, Malaysia and China it goes by the name "bayam".

Orally, amaranth is used for the treatment of ulcers, diarrhea, and inflammation of the mouth and throat. It is also used orally to treat hypercholesterolemia and for the treatment of impure skin. The following substances are listed in the literature as actives of the plant: amaranthin, rutin (quercetin-3-rutinoside) and two other yet unidentified complex glycosides derived from quercetin. Amaranthin is not a flavonoid but an indole-based betaine with two sugar moieties linked to it (one is a hexuronic acid).

**Khella (Visnaga vera)**

Khella grows in the Mediterranean countries, but has also been brought to the Middle East and South America. Khella is commercially cultivated in the United States. It is used in local medicine for the treatment of bronchitis, coughs, high blood pressure, problems with the liver and gallbladder, but most of all for coronary diseases. It fortifies the arteries and is known to act on irregular heartbeat. In the treatment of kidney stones it assists in relaxing the ducts to the bladder, allowing the stones to pass.

The principal active ingredient in khella extract is khelline (visamine), present in 0.3-0.4%. Khelline has outspoken vasodilatory and vasoprotective properties, and therefore khella extract is most suitable for the treatment of couperosis.

Next to khelline a wide variety of other flavonoids are present, more specifically myricetin-3-glucoside, myricetin-3-rhamnoglucoside, rutin, isoquercetin, kaempferol-3-rutinoside and astra-galin.

Also flavonoids structurally related to khelline (which has a psoralen structure) are present, to be mentioned visnadin, samidin, dihydrosamidin, visnagin, visamnidin, visnagenin and visnagidin.

Khella extract is not subject to restrictions for use in personal care and cosmetic products, which is surprising given its potential. Khella extract shall not be used in daytime cosmetics, but preferably in night care cosmetics or in products such as masks.
Ginkgo (Ginkgo biloba)

Ginkgo biloba, also named maidenhair tree, is the last member of the Ginkgoaceae which had their first appearance on Mother Earth some 200-250 million years ago. Darwin named it a living fossil. Ginkgo contains some unusual chemical substances that are found nowhere else in nature: bilobalide (a sesquiterpene), ginkgolides (diterpenes with 20 carbon atoms) and aromatic products such as ginkgol, bilobodol and ginkgolic acid. Little is known about the physiological effects of these substances, although ginkgo extracts are used in traditional medicine for 4000 years for the treatment of a variety of disorders and complaints. Ginkgo biloba extract is also a valuable source for shikimic acid, a building block for the synthesis of flavonoids, in a comparable fashion as phenylalanine.

Ginkgo extract is also a very rich source for flavonoids. The extract contains quercetin, isoquerceinctin, isorhamnetin, kaempferol, myricetin, bilobetin (only one source known, and this is also valid for ginkgetin and isoginkgetin), sciadopitysin.

Also a variety of glycosides is present such as quercetin-3-rhamnoglucoside, kaempferol-3-rhamnoglucoside, quercetin coumaroyl glucoside, kaempferol coumaroyl glucorhamnoside, luteolin glucoside and leuco-anthocyanins.

A number of catechins is present such as catechin, epicatechin, gallocatechin and epigallocatechin.

Catechins also belong to the group of flavonoids, but lack (compared to flavanones) the carbonyl group on the 4-position (catechins can be considered as "hydrogenated anthocyanidins"). Because of the saturation of the \( \Delta^2-3 \) double bond a chiral center is present on the 3-position. Both enantiomers do occur naturally.

Traditionally the ginkgo extract is used to combat disorders of the bronchial tubes. For personal care and cosmetic products enzyme inhibition is the keyword.

The extract of Ginkgo biloba is probably the strongest botanical enzyme inhibitor known; a wide variety of publications on this topic have appeared in the scientific literature. The extract inhibits various elastases, the seven hyaluronidases known and a wide variety of phosphatases. These enzymes exhibit an increasing activity with increasing age, and result in visible signs of ageing. Consistent use of the ginkgo extract will notably reduce these effects, and can therefore be considered as a superior anti-ageing product. Other cosmetically significant properties of the ginkgo extract are vasodilatation and the stimulating effects. There is sufficient reason to believe that these properties boil down to enzyme
inhibition by flavonoids. Also the anti-oxidant properties (the ability to quench free radicals) of the ginkgo extract are important, and an important tool to avoid peroxidation of membrane lipids as well as oxidative stress.

**Calendula (Calendula Officinalis)**

Calendula extract, or calendula oil, is probably the most spirited advocate of homeopathy. This is largely attributed to a wide range of terpenoids present, but also to flavonoids that occur both in calendula extract and calendula oil. These have anti-inflammatory properties, are appreciated irritation quenchers, and have antiseptic, astringent, fungicide, soothing, wound healing and tonifying properties. Quercetin is the most important flavonoid present, next to a wide range of glycosides of quercetin and isorhamnetin. Kalvatchev (14) showed that organic extracts of dried calendula flowers inhibit HIV-1 reverse transcriptase, while aqueous extracts did not show this property. For this reason the flavonoids present in this extract are examined on the potential application for the treatment of HIV infections, although their mode of action is not understood. Quercetin is without doubt the most widespread flavonoid that is known. It indeed is a powerful anti-oxidant, but it is also a powerful enzyme inhibitor, in particular for phosphodiesterases and lipases.

**Licorice (Glycyrrhiza glabra)**

Licorice extract is a powerful extract, and the basis for that is the presence of quite a number of flavonoids: glabradine, liquiritine, isoliquiritine, liquiritigenin, isolumiquiriti-genine, isoliquiritide, diglucoliquiritoside, and some coumarins (umbelliferone and hemiarin). Licorice extract is also used in food industry to make children's sweets.

One of the major functionalities from licorice extract is the inhibition of two enzymes: tyrosinase and superoxide dismutase. This inhibition results in a scenario whereby skin lightening can be achieved while reducing simultaneously reducing oxidative stress. This goes hand-in-hand with the stimulation of the enzyme squalene monooxygenase to promote the topical production of cholesterol. Licorice has also bacteriostatic properties that originate from the flavonoid formononetin (7-hydroxy-4'-methoxyisoflavone).

Glabradine has been identified as the most active flavonoid. It is, in chemical terminology, a catechin. The heterocyclic 6-membered ring on the 7,8-position is composed of an isoprene unit that originates from reaction with dimethylallyl pyrophosphate (DMAPP). Two additional flavonoids are present that are structurally related to glabradin (glabrol, formononetin) that are also physiologically active.

**Horse Chestnut (Aesculus Hippocastanum)**

Horse chestnut is a powerful source for flavonoids. The flavonoid composition is dependant on the part of the tree that is considered. The bark contains 3% aesculin (camarin glycoside), aesculetin, aescin, fraxin, scopolin, fraxetin, sco-
poletin, quercitrin, quercetin and leukoanthocya-

des. The flowers contain kaempferol-3-glucosi-
de, kaempferol-3-arabinoside, kaempferol-3-
rhamnoglycoside, rutin, and isoquercetin. The
seed contains only a minor amount of flavo-
noids, but the leaves are rich in fraxin and sco-
polin.

A major property of horse chestnut extract is to
activate those enzymes that are responsible for
stimulation of the hair follicle. Consequently the
extract is frequently used for hair growth prepa-
rations. Another significant property of the fla-

vonoids present in horse chestnut is the ability to
eliminate build-up of body liquids. The applica-
tion of a gel containing 5-10% horse chestnut
extract to the legs after an intercon-

ntional flight will resolve the edema in 10-15 minutes.

THE MOST SIGNIFICANT

FLAVONOIDS

It has been demonstrated that flavonoids are
indispensable products that shall be part of the
daily diet, but they are highly functional ingre-
dients for personal care and cosmetic products.
A healthy skin will cover a healthy organism.
For this reason it is useful to discuss the major
flavonoids separately.

Quercetin: 3,3',4',5,7-pentahy-
droxyflavone

Quercetin (synonyms: meletin, sophoretin, quer-
cetol, xanthaurine, CI 75670, Natural Yellow 10)
is a high melting, yellow solid (316-317°C). It
is poorly soluble in water (both cold and warm),
but soluble in warm ethanol and acetone.
Quercetin is also soluble in acetic acid, organic
amines and in alkali. Solutions of quercetin in
alkali are intense yellow. However, because of
the limited solubility in commonly used solvents
applied in cosmetic products complete dissolu-
tion may occasionally cause formulation pro-
blems in terms of bio-availability. This problem
can be bypassed to molecularly dissolving querc-
etin in a liquid crystalline matrix composed of
particular amphiphilic products (emulsifiers).
Quercetin is a powerful anti-oxidant suitable for
application in food products. The anti-oxidant
properties of flavonoids are easily understood
because of the presence of a large number of
phenolic hydroxy groups, enabling free radicals
leapfrogging over the aromatic system. As an
example, the anti-oxidant properties of quercetin
enable a much better utilization of ascorbic acid
(vitamin C), having said that ascorbic acid is an
antioxidant by itself.

Quercetin is 20 times more potent than ascorbic
acid, and 50 times more potent than tocopherol
(vitamin E). It has also been demonstrated that
quercetin is able to avoid oxidation of membra-
ne lipids (usually with a high degree of unsatura-
tion) and to reduce oxidative stress.

In a number of publications synergistic mixtures
have been suggested of quercetin with either
ascorbic acid or β-glucans, or a combination of
these three ingredients, taking advantage of the
re-enforcement of the auto-immune system by
β-glucans. Contrary to statements in earlier
publications it is probably not possible to use
quercetin to guarantee the oxidative stability of
ascorbic acid in cosmetic emulsions.

In a way flavonoids, and quercetin in particular,
can be compared to vitamins. Quercetin has been
identified as a positive or negative cofactor for a
number of enzymes. For both vitamins and fla-

vonoids is valid that the human body is not able
to produce them (with the exception of vitamin
D3 and D4) and is dependant on them via the
intake of food. The average daily intake of flavo-
noids (in mg) is given in table XIII.

Given the oral intake of relatively large amounts
of flavonoids accumulative and toxicological
effects have been studied in detail. Schneider
(15) showed that Eubacterium ramulus (which
occurs in human faeces) degrades quercetin (and
also rutin, kaempferol, luteolin, luteolin-7-glucoside, eriodictyol, naringenin, taxifolin and phloretin) to phenolic acids, in the case of quercetin to 2,4,6-trihydroxybenzoic acid.

The FDA has nominated quercetin for toxicity and carcinogenicity studies in the rat as quercetin is subject to a considerable dietary intake. The study was done via a two year feeding study on male and female F344/N rats. The results indicate that there is no evidence of toxic and/or carcinogenic activity in female rats, and that there was only minor and insignificant evidence on male rats, receiving 1.000, 10.000 and 40.000 ppm (max.4%).

Quercetin is a powerful enzyme manipulator. Thorne et.al. (16) demonstrated that quercetin selectively inhibits the activity of A5-lipoxigenase and other enzymes known to be involved in the metabolism of arachidonic acid in cells. Quercetin exhibits both allergic mediator release activity and selective inhibition of the biosynthesis of pro-inflammatory arachidonic acid metabolites, and is a prototype for the development of new anti-allergic and anti-inflammatory compounds. These properties make quercetin to a highly desired product for cosmetic products.

Castelli (17) showed that a combination of ginkgo extract and carboxy-methyl-1,3-β-glucan applied to the skin for two weeks significantly reduced dermatitis for a number of allergens for a large group of woman in a double blind study. Analysis by GC/MS showed that quercetin and, to a lesser extent, kaempferol were responsible for the observations.

In addition, Kim (18) showed that the flavonoids present in ginkgo extract stimulates proliferation of human skin fibroplasts and increase the production of collagen and extracellular fibronectin. Quercetin is heavily involved in this process, next to ginkgolide, bilobalide, kaempferol and sciadopitysin, and that both observations boil down to enzyme inhibition.

Quercetin showed to be potent in the cytotoxicity against tumor cell lines. Scambia et. al. (19) demonstrated that quercetin inhibits the growth of several cancer line cells and that the anti-proliferative activity is mediated by a so-called type II estrogen binding site. Many other flavonoids also have estrogen properties, but quercetin is believed to be one of the more potent products, comparable to genistein.

It was remarkable that quercetin showed itself to be a strong synergist for cis-platinum relative to the anti-proliferative effects of the ovarian cancer cell line OVCA-433. The effects observed were demonstrated to originate from enzyme inhibition.

**Quercetin Glycosides**

Next to quercetin, an aglycon, also a wide variety of glycosides are known, many of them being physiologically active products. The hydroxy group on the 3-position of quercetin may be occupied by a rutinose unit (6-(β-1-l-rhamnosi-do)-d-glucose) and is named rutin (quercetin-3-rutinose).

Rutin may be extracted from Dimorphandra mollis and Ruta graveolens (Rue).

| Table XIII |
| Average human daily intake of flavonoids. |
| Quercetin | 8,5 |
| Rutin | 1,5 |
| Fisetin | 0,4 |
| Eriodictyol | 0,3 |
| Kaempferol | 5,0 |
| Myricetin | 0,6 |
| Luteolin | 0,3 |
| Myricitrin | 0,01 |
Historically rue has been used by thousands of women in Latin America as a contraceptive to prevent pregnancy. It is known that rutin responds positively to the calcium and magnesium metabolism, and has potential benefits for the treatment of osteoporosis.

Rutin has been reported to have anti-oxidant properties and is vital in its ability to improve capillary fragility (increasing the strength of capillary blood vessels) and to regulate their permeability.

Rutin has synergistic activity with ascorbic acid in keeping collagen in healthy condition and to enable proper absorption and use of ascorbic acid. Rutin inhibits the degradation of collagen by the enzyme xanthinoxidase to smaller peptides, and has been shown to reduce the activity of lipoxigenase (tested on soybean lipoxigenase). Quercitrin is characterised as the 3-rhamnoside of quercetin. Quercitrin may occur in either anhydrous form (MP=250°C) or monohydrate (MP=182°C). It is insoluble in cold water but soluble in hot water. It is also soluble in glacial acetic acid, ethanol and in alkaline solution. Alkaline solutions of quercitrin are very intense yellow coloured, and may develop a precipitate in time due to hydrolysis of the glucoside.

Quercitrin is a powerful anti-oxidant. Quercitrin is well tolerated in the gastro-intestinal tract. Dong et al. (20) showed that quercitrin is degraded to either quercetin and rhamnose, but also further degradation (under anaerobic conditions) occurred, resulting in the formation of 3,4-dihydroxyphenylacetic acid and 4-hydroxybenzoic acid. Both products were identified as the metabolites. 3,4-Dihydroxyphenylacetic acid and 4-hydroxyphenylacetic acid are potent in vitro anti-platelet aggregation activitors.

Polygonum fagopyrum (Buckwheat) is an important source for quercitrin. The dried leaves contain 3-8% flavonoids, the majority being quercitrin and rutin. Significant amounts of quercitrin are also found in citrus fruits and in rose hips.

According to a joint Canadian/United States research program quercitrin has been claimed to be promising for the treatment of various forms of cancer. This would include prostate cancer, lung cancer, melanoma and breast cancer (results presented on the 219th national meeting of the American Chemical Society). Tangeretin, nobiletin and quercitin, flavonoids present in tangerine juice, were the most effective inhibitors of human prostate cancer cells. These products also inhibited the growth of melanoma cells and were effective against breast cancer cells, with comparable activity as tamoxifen (anti-breast cancer drug). Animal studies are to date not completed yet.

Quercitrin is useful in the treatment of high blood pressure due to their capillary-strengthening and blood vessel dilating properties. It is also useful in capillary fragility disorders such as easy bruising, bleeding of the gums, and also in circulatory disorders of the retina of the eye. It is particularly useful in the treatment of vein and capillary problems such as varicose veins, venous insufficiency (poor return of blood to the heart from the veins of the legs), and eye problems such as diabetic retinopathy and macular degeneration.

Hyperoside (hyperin, quercetin-3-galactoside) is found in Hypericum perforatum (St.John’s wort). Hyperoside is a powerful anti-ageing product because of the inhibition of the enzyme elastase. Combined with chickweed the extract of St.John’s wort is useful for the treatment of eczema. Hawthorn (Crataegus pinnatifida) is a thorny tree, widely distributed in the north temperate regions. It is an important source of hyperoside, next to protocatechueic and chlorogenic acid, epicatechin, quercetin, isoquercetin and rutin. The psoralen level is low. Also loquat (Eriobotrya Japonica) is a valuable source of hyperoside. Hawthorn and loquat show efficacy on the suppression on the inhibitory effect on Cu²⁺ media-
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Hyperoside has bactericidal properties (MIC=250-500 µg/ml) and has been reported as an anti-viral. It is used to treat fragility of the capillaries (couperosis), dermatitis, has anti-inflammatory properties and is cancer preventive. Isoquercetin (quercetin-3-glucoside) is found in significant amounts in Equisetum arvense (horsetail). The hollow, jointed stems of this flowerless plant contain large amounts of water-soluble (5-8%) with excellent bio-availability. Horsetail reduces the risk of excessive bleeding and contributes to the building of healthy blood cells. Topically applied it has positive impact on the bloodstream. It has been shown that horsetail increases the number of phagocytes, germ-killing enzymes, greatly improving the well-functioning of the entire immune system. Isoquercetin is frequently outperforming β-glucans on the protection of the auto-immune system.

Horsetail contains a significant amount of isoquercetin (up to 0.5%), next to two flavone glycosides characteristic for horsetail (galuteolin & equisetrin). The combination of these flavonoids is responsible for the bactericidal properties. Like most flavonoids, isoquercetin is a powerful anti-oxidant.

Isoquercetin is a well-known aldose-reductase inhibitor. It has also antibiotic and diuretic properties. Some sources for isoquercetin are Filipendula ulmaria (meadowsweet), Foeniculum vulgare (fennel), psidium guajeva (guava) and Viscum album (mistletoe).

CONCLUSION

Flavonoids comprise a large group of products that have similar structural properties. All flavonoids are from vegetable origin; many botanical extracts contain significant amounts of flavonoids. In many cases the functionality of botanical extracts is dedicated to flavonoids. Flavonoids are powerful antioxidants, and in virtually all cases they outperform artificial antioxidants and poor antioxidants such as tocopherol and ascorbic acid. They enable to control oxidative stress and peroxidation of membrane lipids.

Flavonoids are powerful enzyme modulators; in many cases it has been shown that they are positive or negative cofactors for various enzymes such as phosphodiesterases, hyaluronidases, elastases, aldose reductases, lipoxydases and lipoxygenases.

The application of flavonoids in pharmacy/medical technology and food supplements has been well developed. The application of flavonoids in personal care and cosmetic products is less developed, although the use of botanical products is common practice. Major applications of flavonoids are in anti-ageing, anti-cellulite, anti-couperosis and skin lightening products, and applications as soothing, astringency, bactericide properties, and many others.

The use of purified flavonoids has a significant potential in personal care and cosmetics as the application of botanical extracts will never enable to reach a cosmeceutical level of activity. This goes together with the fact that raising the concentration of botanical extracts in consumer products implicitly means also an increased level of less desired products (e.g. alkaloids and saponines) present in the final consumer product. A number of flavonoids are commercially available, such as quercetin, quercitrin, isoquercetin, axigenin, biochanin, genisteine, daidzein and rutin.

The beneficial properties of the use of pure flavonoids start to be recognised by the personal care and cosmetics industry. The first consumer products have already arrived in the market place.
References


Suggested for further reading


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