Clinics in Dermatology (2008) **26**, 347–357

Clinics in Dermatology

Flavonoids as components of biologically active cosmeceuticals

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Abstract Flavonoids are multi-active components used in common cosmetics primarily for antioxidant and soothing actions. Despite this, their multi-active properties are far from being fully used. It is well known that many flavonoids provide protection from telangiectasias and petechias caused by ruptured blood vessels. Thus, the notion of a "strengthening" effect of these compounds on blood vessel walls is common. The activity of flavonoids on skin blood vessels is complex. Three main components of their activity can be distinguished: blood vessel protection, platelet aggregation prevention, and capillary permeability decrease. Each of these components is realized with the participation of several mechanisms differing on the types of receptors that the flavonoids affect. Some of them consist of a direct action on the enzymes responsible for the synthesis of substances of tissue hormone character, such as thromboxanes, histamine, or platelet activating factor. The mechanisms based on less or more indirect activity can also be met. At least 11 points for activity can be distinguished among flavonoids' actions on blood vessels.
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Introduction

The specific feature of modern skin care cosmetics is multi-activity enabling multidirectional complex effects, even in relatively simple formulations. The perfect example is the biologic effects of the most often used cosmetic procedure: covering the epidermis with a hydrolipid occlusion layer or different forms of antiradical protection. The meaning of cosmetic multi-activity is coded in a legal definition of the use of cosmetic products: "maintaining (the skin) in good condition."[1] It is understandable that the manufacturers of active products pay attention to multi-active products, which act on different receptor systems and provide complex care effects as a result of this action. Such substances can be found in many natural raw materials, especially of plant origin. These compounds are polyunsaturated fatty acids, diterpenes and triterpenes, some saponins, sterols, and one of the most popular class of natural compounds, flavonoids.

Flavonoids are the largest group among plants with active properties; more than 5000 flavonoids have been extracted and identified. Many publications have described flavonoids and their activity.[2-5] The chemical structure of flavonoids belong to the derivatives of 1,3-diphenylpropan-1-one (chalcone); the best known groups are the cyclic compounds containing the phenylchromone system (benzo-gamma-pyrone) (Fig. 1).

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doi:10.1016/j.clindermatol.2008.01.004

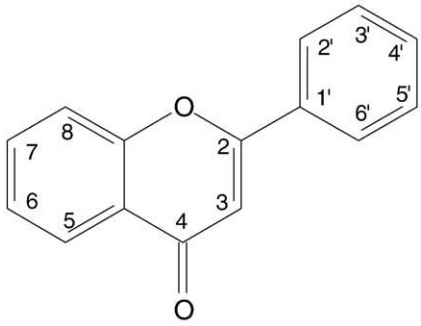
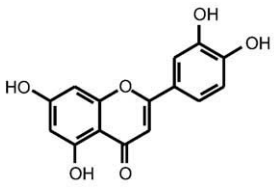


Fig. 1 Flavone (benzo-gamma-pyrone).

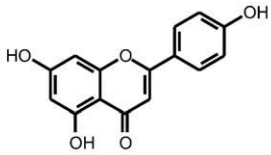
In most flavone derivatives, the phenyl ring is usually in the 2 position. The compounds containing the phenyl ring in the 3 position also belong to flavonoids; they are called isoflavonoids. The nomenclature of flavonoids is complex; in many cases, the commonly used names are ambiguous.[2]

Depending on the chemical structure, the following group of flavonoids can be distinguished:

Flavones (luteolin and apigenin)

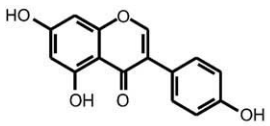


luteolin

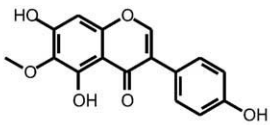


apigenin

Isoflavones (genistein and tectorigenin)

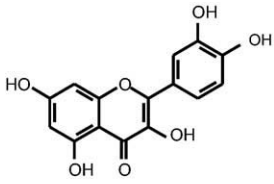


genistein

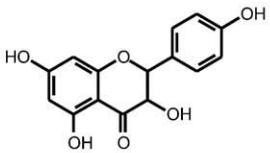


tectorigenin

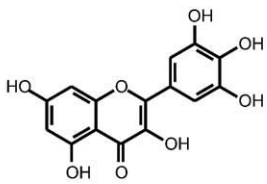
Flavonols (quercetin, kaempferol, and myricetin)



quercetin

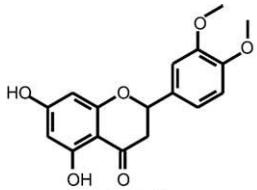


kaempferol

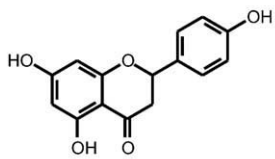


myricetin

Flavanones (hesperetin, naringenin)

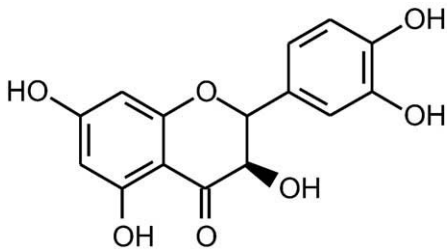


hesperetin



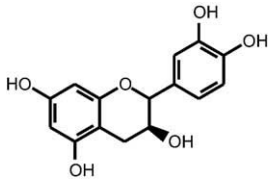
naringenin

Flavanones (taxifolin)

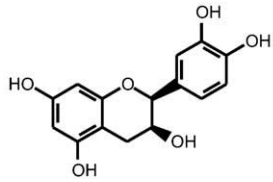


taxifolin

Flavan-3-ols (catechin and epicatechin)

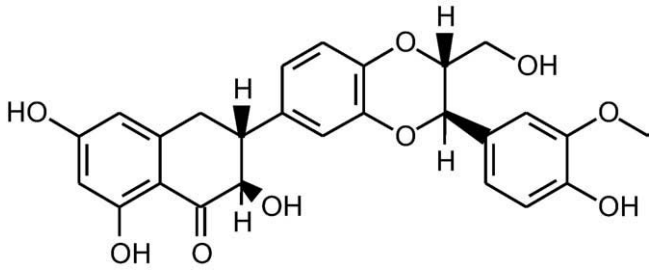


catechin



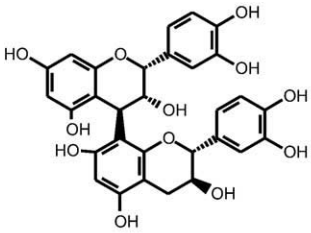
epicatechin

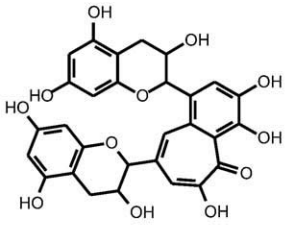
Flavonoids of complex structure (silybin)

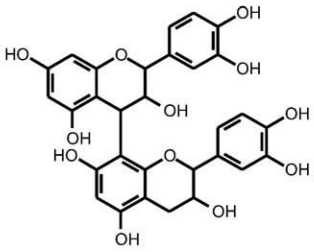


Sylibin

Oligomers (built from two to three molecules of flavan-3-ols) (tannins, theaflavins, proanthocyanidins)







In nature, flavonoids are present in the form of glycosides (sometimes called bioflavonoids). Flavonoid glycosides are built of actual flavonoid (aglycon) and hydrocarbon, from which disaccharide rutinose (D-glucose bound to L-rhamnose) and monosaccharide rhamnose are the most common. Some examples of aglycons and the corresponding glycosides are the pairs: quercetin/rutin and diosmetin/diosmin.

Because of the presence of sugar residue, the glycosides usually exhibit good solubility in water; free flavonoids are water insoluble (or soluble poorly), but they dissolve in organic solvents. The glycosides are susceptible to hydrolysis in acidic solutions with aglycon release. They also undergo enzymatic hydrolysis, but there is a lack of data concerning these types of processes in the skin.

In medical practice, a synthetic derivative of rutin is used: troxerutin. In the structure of troxerutin, part of the hydroxyl groups is blocked by hydroxyethyl residues and diosmin, which is known to protect blood vessels twofold more than troxerutin.

Flavonoids are present in all angiospermous and many gymnospermous plants. They can be present in different parts of plants, from blossoms to root systems. They have complex and often unknown biologic functions, mainly as antioxidants protecting from free radical-initiated autooxidation and as flower dyes attracting insects. Many compounds of this group inhibit the growth of microorganisms, protecting plant tissue from infections. Others are responsible for unpleasant taste, protecting plants from being eaten by animals. Relatively poorly investigated among flavonoid functions is their activity as peculiar interspecies and intraspecies transmitters of information concerning symbiotic processes and other forms of contact with the soil environment.

Flavonoid activity in mammals

Despite their plant origin, flavonoids exhibit a remarkable wide spectrum of activity toward mammals' organisms because of nonspecific physicochemical activity and their affinity for the number of tissue receptors. To some approximation, the range of biologic activity of flavonoids can be presented as follows[4]:

Nonspecific activity
- Absorption of ultraviolet radiation
- Reactive oxygen species neutralization
- Inhibition of radical reactions
- Metal chelation
- Inhibition of enzymes

Specific activity
- Affinity to estrogenic receptors
- Anti-inflammatory activity (various mechanisms)
- Impact on cardiovascular system (various mechanisms)
- Influence on regulatory systems and tissue signals transmission

Other
- Microorganism growth inhibition

In the form of plant extracts, flavonoids have been used in dermatology and cosmetics for a long time. However, the mechanisms of their actions have been discovered relatively recently. The permeation of flavonoids through the skin barrier is poorly investigated; the available data indicate that the compounds of this group permeate through the stratum corneum and can reach the viable layers of the epidermis and dermis.[6,7] The permeation rate depends on the flavonoid's structure and vehiculum composition.[8]

Antiradical properties

The best-known flavonoid activity on the skin is linked to its antiradical properties. Most flavonoids containing phenol groups possess a relatively high reduction potential and forms of resonance-stabilized anion radicals. Fig. 2 presents an example of a stable radical anion.

The scavenging activity of flavonoids depends to a high degree on their structures and physicochemical properties (ie, logP).[9] In commonly used plant extracts there are always mixtures of many compounds belonging to this group that are present in the form of aglycones and lipophilic glycosides. This allows a wide spectrum of antiradical activity; commonly used natural mixtures of flavonoids scavenge nearly all kinds of free radicals and reactive oxygen species. A high affinity of these compounds

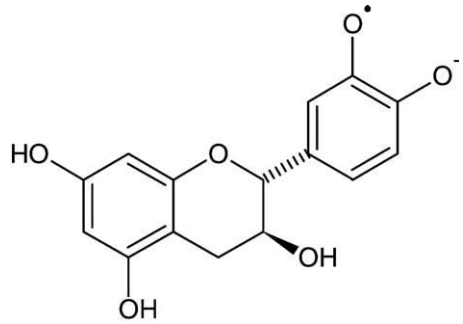


Fig. 2 Catechin radical anion.

toward singlet oxygen and the ability to reduce tocopheryl and tocotrienol anion radicals is of particular importance. Flavonoids extracted from green tea leaves and seeds, leaves of wine grapes, and the oligomers of these compounds present in a bark of Mediterranean pine (pycnogenols) are considered to protect the skin against radical stress most effectively. The antiradical activity of flavonoids is supported by the ability of ultraviolet radiation absorption in the wide range, with maximum far ultraviolet B (250–280 nm) and A (350–385 nm).

Because of the relatively low values of absorbance, the effects obtained at the commonly used concentrations are insignificant. In this sense, the activity could be considered as adjunctive. Similar to other natural compounds, flavonoids cannot replace traditional synthetic sunscreens.

Metal complexation

Flavonoids are capable of metal complexation; in particular, they form chelates with bivalent metals.[4] The metal-complexing sites within a flavonoid structure are hydroxyls at C-3, C-5, and C-3, and carbonyl group at position 4. The share of particular structures depends on the pH: An increase in pH leads to an increase in the stability of these chelate structures, in which hydroxyls at C-5 and C-3 take part.[10] The products of flavonoid oxidation, anion radicals of semiquinone structure, exhibit strong chelating properties, especially toward Mg^{2+} and Zn^{2+} ions. The ability of transition metal complexing is an important factor for the biologic activity of these compounds. Flavonoids and the products of their oxidation compete with metalloenzymes' proteins and inhibit many metabolic pathways.

The binding of transfer metals influences many oxidative processes, including the reactions from radical stress. A particular case is the inhibition of low-density lipoprotein oxidation and destructive oxidative processes occurring with the participation of nucleic acids.[11,12]

The ability of transition metal chelation is an important factor influencing the anti-aging activity of flavonoids, but also for many other activity directions; it plays a crucial role in the impact on capillary blood vessel and inhibition of inflammation propagation.

Many flavonoids exhibit an affinity toward protein structures. These interactions, on the molecular level, can be divided into two groups:

- Interactions of van der Waals type, between aromatic rings and lipophilic amino acid residues. Such bonds are particularly preferred in case of planar, polarizable structures of isoflavones and flavonols, in which delocalization of electrons within all three rings occurs.[13]
- Hydrogen bonds between hydroxyl or ketone groups of flavonoids and carbonyl or hydroxyl groups of protein chains. The strength of the bond depends on proton acidity, which is especially high in flavones and flavonols. To the particular case belong the compounds containing carbonyl group at position 4, which increase the acidity of hydroxyl groups at position 7 leading to partial dissociation and ionic bond formation with basic amino acid residues.[10,14]

Because of the specific protein structure (alongside structures capable of hydrogen bond formation and hydrophobic cavities), the specificity of individual protein bonding is low.

Protein binding

The consequence of flavonoids' affinity toward protein structures is their wide spectrum of biologic activity. The simplest is astringency, which is well visible in plant extracts (particularly those containing catechins and their derivatives) when applied on the skin surface and mucous membranes. The interactions of flavonoids with adenosine triphosphate-binding proteins,[15] protein receptors of nervous system, enzymes such as oxygenases and cyclooxygenases, and some oxydases and monooxygenases of cytochrome P450 isoforms have more complex effects. This is broadly discussed in the review by Dangles and Dufour.[16]

In regard to cosmetic activity, one of the essential effects of flavonoids binding to proteins is their affinity to estrogenic receptors of both types (α and β). Isoflavones act strongly. The affinity of genistein to estrogenic receptor-α and β is estimated as 0.7% and 13.0% of 17β-estradiol affinity, respectively. Genistein or other flavonoid binding evokes the dimerization of the receptor and appropriate gene induction. Thus, this activity is analogous to typical estrogen activity. Relatively low activity (estimated in relation to estrogenic receptor-α and β as 0.025% and 0.8%, respectively, of 17β-estradiol activity) is compensated by a greater plasma concentration of the active property.[17,18] Flavones

(eg, kaemferol and apigenin) exhibit similar, although much weaker, activity.

Anti-inflammatory activity

The multi-activity of flavonoids is also manifested in their anti-inflammatory activity. This action is widely used in cosmetology. Most plant extracts that are used with the purpose of soothing or decreasing the irritation potential of various raw materials of cosmetics contain flavonoids. The activity of these compounds results from their complex interactions with proinflammatory factors and enzymes directly or indirectly participating in the generation or propagation of inflammatory stages. Flavonoids, because of their ability to scavenge free radicals, inhibit the oxidative processes of membrane lipids, which lead to arachidonic acid release.[19] At the same time, because of their affinity to proteins and metals, chelation flavonoids (eg, apigenin glycosides present in chamomile) inactivate 5-lipoxygenase and cyclooxygenase, which play a key role in arachidonic acid transformation into proinflammatory leukotrienes (LTs) and prostaglandins.[20] Another mechanism of activity is related to the inhibition of enzymes linked to cell activation and secretion of regulatory substances propagating the inflammatory stage in a tissue: tumor necrosis factor-α and other cytokines. It has been demonstrated that a number of flavonoids influence the synthesis and release of nitric oxide, the substance that is responsible for the regulation of many physiologic functions, including evoking and propagating inflammation.[21,22]

The influence of flavonoids on blood vessels plays an important role in their anti-inflammatory and anti-irritant activities. Flavonoids decrease tissue congestion and exhibit strong antiedematous activity. Thus, flavonoids reduce inflammatory symptoms.

Antimicrobial activity

The activity against microorganisms is the next important element of the biologic activity of flavonoids.[2] Many flavonoids exhibit antibacterial and antifungal activities. One of the important functions these compounds have in plants is protection against infections caused by viruses, bacteria, and fungi. The activity is not limited to phytopathogenic microorganisms and could be applied to skin protection. One of the most important elements of the activity is antiviral activity. Flavonoids belong to the sparse group of compounds that selectively inhibit the proliferation of such viruses as herpes simplex, polio, and pseudorabies. A number of synthetic derivatives (eg, quercetin dimethyl ether) also exhibit antiviral activity.

Despite numerous experiments, there is still a lack of literature data concerning the structure and activity relationship. In some plant extracts, biocidal activity against higher organisms (ie, schistosomiasis) was proved.

Protective effect on blood vessel walls

It is well known that many flavonoids provide protection from telangiectasias and petechias caused by ruptured blood vessels. Thus, the notion of a "strengthening" effect of these compounds on blood vessel walls is common. In medicine, there is a term for the resistance of blood vessels. Reduced resistance of blood vessels is manifested in their excessive fragility, ability to rupture, and susceptibility to subcutaneous extravasation of blood. In practice, the decrease in blood vessel resistance is determined by the decrease in so-called critical petechial pressure, which when exerted on a given skin surface in a defined time leads to blood vessel rupturing.

Flavonoids (especially rutin and its derivatives) exhibit a protective effect on blood vessel walls. In case of hesperidin deficiency, capillary fragility increases significantly, but the changes regress after supplementation with flavonoids.[23] Catechin, epicatechin, and hesperetin show similar activity.[24]

Several fundamental mechanisms of flavonoids' protective activity can be distinguished:

1. Influence on neutrophils
2. Protection of vitamin C
3. Inhibition of collagen activity and elastin-degrading metalloproteinases
4. Prevention of adrenaline oxidation

Influence on neutrophilic granulocytes

Neutrophils are blood cells specializing in detecting and phagocytizing bacteria and dead cell residues in wounded or infected tissues. Neutrophilic granulocytes can damage angioendothelium forming (ie, capillary walls). The damages are evoked by singlet oxygen and unstable oxygen radicals produced by granulocytes during the phagocytose process.

The protective effect of flavonoids on endothelium is indirect and linked to the widely known antiradical activity of flavonoids and neutralization of free radicals formed during phagocytosis.

Vitamin C protection

The presence of vitamin C is necessary for the proper synthesis of collagen, including collagen-building blood vessel walls. Collagen synthesis disorders will lead to an abnormality in blood vessel structure and in most cases to a decrease in their resistance. One of the main factors responsible for vitamin C

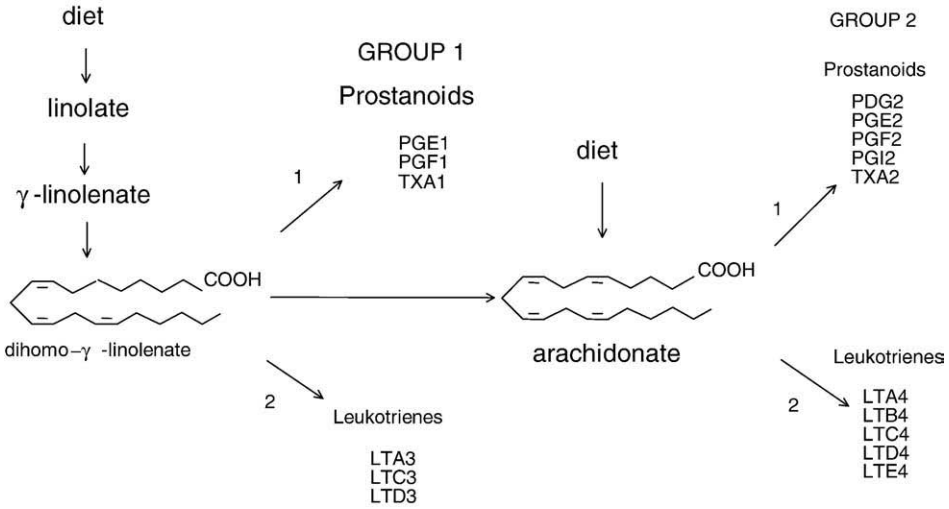


Fig. 3 Pathways of synthesis of eicosanoids from linoleic and arachidonic acids: A, cyclooxygenase enzyme; B, lipoxygenase enzyme. Borrowed with permission from Murray RK, Granner DK, Mayes PA, Rodwell VW. Biochemia harpera. Warsaw: PZWL, 1995:955.

concentration depletion in the skin is free radical activity, especially the radicals as precursors of oxidative processes, because vitamin C is particularly sensitive to oxidation. With their strong antiradical activity, flavonoids prevent vitamin C from decomposition; thus, flavonoids indirectly protect the capillaries' walls.

Inhibition of adrenaline oxidation

Adrenaline is a neurohormone produced locally in nerve endings and simultaneously secreted centrally and transported with blood. Adrenaline's action on nerve receptors in blood vessel walls leads to their contraction. The higher the adrenaline concentration, the longer the contraction is. Maintenance of proper adrenaline concentration is an indirect factor protecting blood vessel walls: Too low of a concentration leads to fast angiectasis. As a result, contractions become shorter and more often. Frequent, alternating contractions and relaxations are stressful for blood vessels, leading to muscular coat "tiredness" and vessel resistance reduction.

Flavonoids inhibit adrenaline autooxidation by complexing iron and copper ions catalyzing this process. As a result, flavonoids prevent oxidation and maintain the concentration at the necessary level to prevent angiectasia. After epicatechin administration, the time of adrenaline-evoked contraction increases three-fold.[25] Thus, epicatechin activity can be considered as an indirect protective activity toward capillary walls.

The effect of prolongation of vessel contraction time by other flavonoids is not obvious. According to other sources, flavonoids as group of compounds exhibit spasmolytic activity. Thus, the effects of adrenaline and flavonoid activity may, at least partially, be counterbalanced.

Prevention of platelet aggregation

The main goal of the platelet aggregation process is to seal the blood vessels and prevent blood loss in case of blood vessel damage. After blood vessel injury, activated platelets adhere to collagen fibers, sealing the blood vessel wall. Platelet sticking may also occur without signals from the injured tissue, and then smaller aggregates are formed that hinder blood flow through the capillaries. Vessel clogging makes it necessary to intensify the flow through neighboring vessels; this can lead to an increase in fluid pressure in the capillaries and an increase in permeability or permanent dilatation and telangiectasias. The next consequence could be vessel rupturing and petechias formation, as well as forming new junctions between arterioles and venules, resulting in worsening of the skin color (excessive redness).

Because of platelet aggregation inhibition, flavonoids indirectly improve the blood flow in vessels, decrease skin redness, and reduce the risk of new angiectasias formation. Platelet aggregation inhibition is a complex activity, and four basic mechanisms can be distinguished:

1. Inhibition of thromboxane (TX)A_2 and TXB_2 synthesis and receptor for TXA_2 blocking
2. Inhibition of fibrin synthesis
3. Inhibition of platelet aggregation factor synthesis
4. Impact on basophilic granulocytes—increase in heparin secretion

The efficacy of individual flavonoids or their mixtures within the scope of prevention from platelet aggregation is described in a number of publications; however, the detailed mechanisms of their activity are not given. Some authors emphasize the high efficacy of flavonols and flavonol-rich plant extracts in the limitation of platelet aggregation.[26]

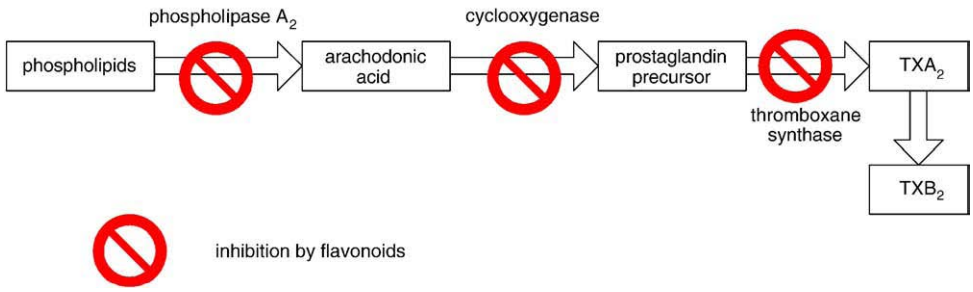


Fig. 4 Influence of flavonoids on TX synthesis.

A synergic activity of quercetin and catechin[27] and quercetin and vitamin C has been described[28] within the scope of platelet aggregation inhibition. This allows the hypothesis that multicomponent plant extracts, widely used in cosmetology, should be particularly effective in this range. However, there is a lack of detailed studies.

Influence on thromboxane synthesis and the receptor for thromboxane A_2

Thromboxanes belong to one of the so-called eicosanoids: tissue hormones regulating many functions in the body. Eicosanoids are synthesized "against order" in places where they are needed. Their living time in the body is short. Thus, they are not transported with blood or lymph, and their activity is solely local. To synthesize eicosanoids, polyunsaturated fatty acids (linoleic, gamma-linolenic, alpha-linolenic, and arachidonic) are necessary (Fig. 3).

TXA_2 and TXB_2 are formed from arachidonic acid (Fig. 4). Both of them take part in blood clotting by influencing platelets and prompting their aggregation. TXA_2 exhibits a stronger physiologic effect. However, TXA_2 is unstable and transforms into TXB_2 during the short time. In regard to TXB_2's influence on platelet aggregation, researchers are not unanimous; some even state that TXB_2 is a physiologically non-active compound.

Flavonoids inhibit TX synthesis just before releasing arachidonic acid, which makes it accessible for further reactions. If there is no demand for eicosanoids of arachidonic acid origin, the acid is stored in the form of phospholipids in cell membranes. Thus, the release of arachidonic acid from phospholipids must be the first stage of TX synthesis. Phospholipase A_2 is responsible for this process, and its activity is inhibited by flavonoids. For the next step of TX synthesis, enzymes are also necessary. These are cyclooxygenase and TX synthases, both of which are inhibited by flavonoids.

The ability of TX synthesis inhibition is different for various flavonoids. It was shown in a number of studies that the following flavonoids exhibit an inhibitory effect: apigenin,[30] luteolin,[31] baicalin,[32] diosmin, hesperidin, naringin, quercetin, and catechin.[33] Rutin, which is widely used in cosmetology, exhibits much weaker activity in this range.[34] However, because of effective Ca^{2+} ion complexation, rutin may improve blood flow in vessels in accordance with the mechanisms of fibrin synthesis given below.[35] As Dehmlow et al[36] proved, silibinin obtained from *Silybum marianum* or other plant extracts (ie, from *Artocarpus communis*)[37] is capable of effectively inhibiting TX synthesis.

TX activity may be reduced indirectly via TXA_2 receptor blocking by flavonoids. In vitro studies proved that flavonoids with a double bond between C3 and C4 and the ketone group at the C4 position show the strongest effect in this scope.[38]

Inhibition of fibrin synthesis

Fibrin is a water-insoluble protein necessary for clot formation. A clot, which supports the sealing made of platelets, is formed after vessel damage from fibrin fibers and erythrocytes, which strengthen its construction. Because clot forming must proceed quickly, there is always a fibrin precursor present in plasma: water-soluble fibrinogen. To transform fibrinogen into fibrin, thrombin presence is necessary. Thus, thrombin synthesis (from prothrombin) must be the first stage in fibrin formation. In this process, the

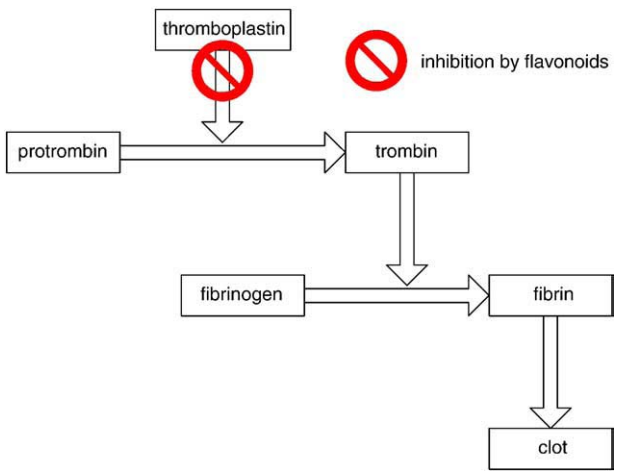


Fig. 5 Influence of flavonoids on fibrin formation.

presence of thromboplastin, the activity of which requires calcium ions, is necessary.

Similar to platelet aggregation, fibroin can be formed in places where the blood vessels remain intact. Fibroin hampers blood flow in capillaries. Flavonoids are capable of calcium ion complexation[35,39] and inhibition of thromboplastin activity, which make it impossible for prothrombin to convert into thrombin. Thus, flavonoids may inhibit fibrin and clot formation (Fig. 5).

Inhibition of platelet activating factor synthesis

Platelet activating factor is an inflammatory mediator produced by platelets, among others. Even its low concentration (10^{-11} mol/dm^3) causes platelet aggregation, and the effect on platelets is similar to TX activity.

Flavonoids inhibit platelet activating factor release from cell membrane phospholipids.[40] Thus, they prevent platelet aggregation and improve blood flow in capillaries.

Effect on basophilic granulocytes

In blood vessel protection, the influence of flavonoids on basophiles is an important factor in blood flow improvement. The essential activity is the increase in heparin synthesis. Heparin is a natural anti-aggregation factor with effects that are different from those of TX and platelet activating factor activity. Moreover, heparin reduces thromboplastin activity and thus hampers fibrin synthesis.

Studies by Alexandrakis and colleagues[41] prove that flavone derivatives increase heparin secretion through the influence on basophiles. Thus, flavone derivatives prevent platelet aggregation and synthesis of fibrin, which participates in clot formation.

Decrease in capillary permeability

An increase in capillary permeability during inflammatory stages or injury results in excessive amounts of plasma release into extracellular spaces, leading to edema. When draining excess fluid by the lymphatic system is hampered, edema may last a long time, resulting in aesthetic problems and pain, for example, leg edemas of those who work for long periods in a standing position. Flavonoids as group of compounds are currently used in different types of preparations to decrease fluid release into tissues (ie, blood vessel "sealing") and in formulations for so-called heavy legs or under-eye bags.

One of the first flavonoidal preparations to protect against excessive blood vessel permeability was citrus fruit peel extract (commonly called citrin in pharmacology), which owes its activity to the presence of hesperidin and eriodixin (demethylated hesperidin). Further studies revealed that rutin and its derivatives effectively reduce blood vessel permeability. At present, O-β-hydroxyethyl-rutosides are used the most often.

The details concerning antiedematous activity of individual flavonoids are not consistent; Harborne and Williams[42] provide a detailed review of publications.

The decrease in blood vessel permeability is a complex action, and several basic mechanisms can be distinguished within its range:

1. Hyaluronidase inhibition
2. Inhibition of inflammatory mediators
3. Histamine release inhibition
4. Inhibition of adrenaline oxidation

Hyaluronidase inhibition

One of the most important components of blood vessel walls is hyaluronic acid, which is decomposed in the body by the enzyme hyaluronidase. It is well known that the permeability of capillary walls depends on the hyaluronic acid content: the less amount of hyaluronic acid, the greater the capillary permeability.

Flavone compounds reduce hyaluronidase activity, thus preventing hyaluronic acid from decomposition and decreasing capillary permeability.

An in vitro study[43] indicated a stronger inhibiting activity of aglycons compared with glycosides (ie, quercetin inhibits hyaluronidase more than rutin). In vivo studies did not confirm these results, in which both groups of flavonoids exhibited similar activity. This may result from glycosides hydrolysis in the body.

The inhibitory effects of plant extracts rich in other biologically active substances, such as triterpenic saponins and sapogenins[44] (*Hedera helix, Aesculus hippocastanum, Ruscus aculeatus*,[15,45] and *Glycyrrhiza glabra*[46]), on hyaluronidase is well known. The inhibitory effect of isolated flavonoids is in general weaker than the activity of flavonoid-rich plant extracts.

Inhibition of inflammatory mediators

Among the eicosanoids synthesized in the body, a group of compounds taking part in inflammatory states can be distinguished: inflammatory mediators. They are responsible for an increase in blood vessel permeability. Most of the known inflammatory mediators are of arachidonic acid origin; these are prostaglandin E_2, LTB_4, LTA_4, LTC_4, LTD_4, LTE_4, TXA_2, and TXB_2, influencing platelet aggregation processes.

Among the inflammatory mediators that increase blood vessel permeability is platelet activating factor, which is not an arachidonic acid metabolite and is released from cell membrane phospholipids. Similar to TX, platelet activating factor participates in blood clotting.

In the process of inflammatory mediators synthesis, two enzymes—cyclooxygenase (catalyzing prostaglandin-2, TXA_2, and TXB_2 formation) and 5-lipoxygenase (catalyzing LTB_4 synthesis)—are involved (Fig. 3). Both enzymes are inhibited by flavonoids. Flavonoids (ie, ginkgetin)[47] and synthetic 2′,4′,7-trimethoxyflavon[48] also inhibit the activity of phospholipase A_2, an enzyme that releases arachidonic acid from phospholipids, making it accessible for further reactions.

The mechanism of 5-lipoxygenase inhibition is relatively well known. For the proper functioning of this enzyme, the presence of Fe^{3+} ions in its structure is essential. Flavonoids are capable of Fe^{3+} ion complexation,[49] resulting in 5-lipoxygenase activity inhibition.

The inhibition of specific inflammatory mediators by individual flavonoids has not been extensively studied. However, it was demonstrated that the effect on mediators formed in different metabolic pathways may be different, that is, silibinin (flavonoid obtained from *Silybum marianum*) reduces the activity of both enzymes but is much stronger in the case of 5-lipoxygenase (LTB_4 production) than in cyclooxygenase.[36] Flavonoids with OH groups at positions 3′ and 4′ exhibit better lipoxygenase inhibition, but the compounds with no OH groups in ring C are more effective in cyclooxygenase activity inhibition.[31,50]

Inhibition of histamine release

Histamine, which is released during inflammation and allergy, courses from the mast cells present in vessels surrounding tissues and basophiles being blood cells and causes a significant increase in vessel permeability.

Quercetin, kaempferol, and myricetin inhibit histamine release from mast cells. A number of flavonoids also influence histamine release from basophiles. In this case, the inhibition is strictly dependent on the flavonoid's structure.[41,51] Only compounds with a ketone group at position 4 and a double-bond C2-C3 in the γ-pyrone ring are active within this scope. Thus, this is the same group of compounds that block the TXA_2 receptor. The hydroxyl group's position also influences the activity.

Glycosides (rutin and naringin) and flavanones (taxifolin and hesperidin) (lack of C2-C3 bond) are inactive. Moreover, cyanidin and catechin, which do not contain the ketone group in their structure, are also inactive.[52] Quercetin is considered to effectively inhibit histamine release. The fact that morin, which differs from quercetin only in OH group configuration in one ring and does not inhibit histamine release, indicates the influence of the OH group's position on flavonoids' activity.[53]

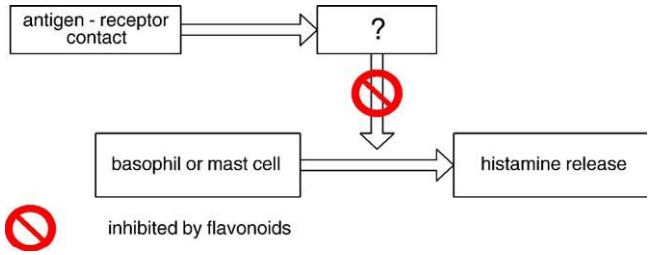


Fig. 6 Influence of flavonoids on histamine release.

The factor that starts the histamine release process is the contact of an antigen with a receptor in the cell membrane of a granulocyte or mast cell. In the next step, the compounds, whose presence leads to histamine release, are released or synthesized. The structures of these compounds have not been determined. The mechanism of histamine release inhibition by flavonoids is linked to flavonoids interacting with these unidentified compounds (Fig. 6).

Inhibition of adrenaline oxidation

During blood vessel contraction, their permeability for plasma decreases. Adrenaline as a shrinking factor directly influences the permeability of blood vessels. Epicatechin, by the inhibition of adrenaline oxidation and lengthening contraction, will indirectly decrease the permeability of blood vessels.

Other flavonoid activity, as in the case of a protective effect on vessel walls, may be weaker because of spasmolytic activity. Angiostenotic activity cannot be, in all cases, connected to vessel sealing. Some compounds cause an increase in their permeability, for example, TXs and LTs.

Conclusions

Flavonoids' activity on skin blood vessels is complex. To simplify, three main activities can be distinguished: 1) protection of blood vessel walls, 2) prevention of platelet aggregation, and 3) decrease in capillary permeability.

Each of these activities is realized with the participation of several mechanisms that differ in the types of receptors on which the flavonoids affect. Some of them consist of a direct action on the enzymes responsible for the synthesis of substances of tissue hormone character, such as TX, histamine, or platelet activating factor. The mechanisms based on less or more indirect activity can also be met. These are the adrenaline oxidation process, hyaluronidase inhibition, and vitamin C protection against oxidative processes. At least 11 points for activity can be distinguished among flavonoids' actions on blood vessels.

There is a lack of data in the literature to unambiguously determine the mechanisms that dominate a specific activity.

The analysis attempts based on the estimation of individual structures' activities have not achieved the desired results because of the small amount of comparable and reliable experimental data.

For these reasons, the determination of relationships between dermatologic or cosmetic effects and the specific point or mechanism of action seems to be impossible. The analysis of the structure–activity relationship shows interesting results. However, the correlations are not useful in practice because of the wide use of incompletely sussed out mixtures of natural compounds and synergistic effects occurring inside the mixtures.

Flavonoids are multi-active components used in common cosmetics primarily for antioxidant and soothing actions. They are also used in some specialized products of antiedemic properties. Despite their multi-active properties, flavonoids are far from being fully used. The goal of this article was to present the possible uses of flavonoids as main active ingredients in cosmeceuticals. One of the most important of these possibilities is the cosmeceutical influence on the skin–blood microcirculation to improve the factor-limiting tissue growth and renewal in all skin types.

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