REVIEW ARTICLE

Journal of Pre-Clinical and Clinical Research 2022, Vol 16, No 3, 99-107
www.jpccr.eu

The role of flavonoids in prevention and treatment of selected skin diseases

Natalia Gębka[1,A-B,D] ✉, Jakub Adamczyk[2,B-D], Barbara Gębka-Kępińska[3,B-D], Elżbieta Mizgała-Izworska[4,E-F]

[1] *Dr. B. Hager Multispecialist County Hospital in Tarnowskie Góry, Poland*
[2] *Academic Centre for Dentistry and Specialized Medicine, School of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland*
[3] *Department of Neurology, School of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland*
[4] *Department of Family Medicine, School of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Gębka N, Adamczyk J, Gębka-Kępińska B, Mizgała-Izworska E. The role of flavonoids in prevention and treatment of selected skin diseases. J Pre-Clin Clin Res. 2022; 16(3): 99–107. doi: 10.26444/jpccr/152551

Abstract

Introduction and Ojective. The skin is the most important external organ, protecting against pathogens, physical and chemical injuries, as well as ultraviolat (UV) radiation. Continuous exposure to UV radiation, allergens, and pollutants, as well as consumption of highly processed foods, all promote the development and exacerbation of skin diseases, which appear highly differentiated. Skin diseases have a significant impact on the patient's quality of life and psychological well-being, which is why finding effective therapeutic compounds appears to be so important, especially since multiple conditions still remain untreated. The benefits of flavonoids in the management of psoriasis, acne, atopic dermatitis, urticaria, ringworm, and other skin diseases, are discussed in this review.

Review methods. A search was conducted using PubMed and Google Scholar databases for articles, to assess the effect of flavonoids in the prevention and treatment of skin diseases. Articles in both Polish and English were searched for. To eliminate duplicate works, the bibliography was reviewed.

Brief description of the state of knowledge. Flavonoids' antioxidant and photoprotective properties are the primary factors influencing their preventive use in the development of skin diseases. The risk of tumour formation is significantly reduced as a result of these two applications. They hasten the healing of long-lasting wounds and ulcers due to their circulation-stimulating properties. Plants high in flavonoids are used in dressings and poultices. Their extracts are used in creams and solutions to treat and prevent a variety of skin diseases.

Summary. The antioxidant and anti-inflammatory effects of flavonoids makes them an important reference in the treatment of skin diseases. The advancement of natural medicinal substances is a critical aspect of modern medicine.

Key words

Atopic Dermatitis, Psoriasis, Acne, Flavonoids, Antioxidation

INTRODUCTION, OBJECTIVE AND METHOD

The increasing prevalence of inflammatory, infectious, allergic and autoimmune skin diseases is observed year after year. This is due to increased exposure to negative environmental factors, the use of household chemicals, and improper nutrition. Currently, it is believed that every third Pole suffers from skin diseases, the most common of which is acne vulgaris, amounting to 80% of all skin diseases [1]. Tinea capitis, psoriasis, atopic dermatitis, untreatable ulcers and skin cancer are also on the rise. The treatment of skin diseases is lengthy due to the lack of rapid and effective treatment methods. Unfortunately, many patients indulge in polytherapy in anticipation of a curative effect. To avoid this, it is necessary to develop new methods of prevention and treatment of chronic skin diseases supported by natural ingredients.

The aim of this review was to analyze the literature on the use of flavonoids in prevention and treatment of selected skin diseases. Using PubMed and Google Scholar databases, as well as books and online journals, a search was conducted for articles published between 2007 – 2022 to assess the effect of flavonoids in the prevention and treatment of skin diseases. Articles in Polish and English were searched for using keywords such as: flavonoids, psoriasis, acne vulgaris, rosacea, atopic dermatitis, allergic urticaria, ringworm, and ulcers, sores, wounds and burns. A review of the bibliography was carried out to eliminate repetitive works. The collected data are summarized, categorized, analyzed, and discussed.

✉ Address for correspondence: Natalia Gębka, Dr. B. Hager Multispecialist County Hospital, Tarnowskie Góry, Poland
E-mail: natalia.gebka@gmail.com

Received: 04.07.2022; accepted: 31.07.2022; first published: 29.08.2022

REVIEW AND DISCUSSION

Flavonoids. Flavonoids are widespread substances of natural origin occurring in the plant world. Composed of two benzene rings and a heterocyclic pyran in between, they take two isometric forms: flavonoid and isoflavonoid. The difference between flavonoids is the number and type of substituents at the last, outermost ring, the number of hydroxyl group positions at the rings, as well as the number of hydroxyl groups forming glycosidic bonds with simple sugars [2, 3]. As the number of hydroxyl groups in the molecule increases, the antioxidant effect is enhanced [2, 4].

Table 1. Division of flavonoids [2]

Group	Links
Flavan-3-ols	catechin, epicatechin,
Anthocyanidins	cyanidine, pelargonidine
Flavonones	naringenin, naringin, hesperetin, hesperidin
Flavone-3-ole	quercetin, kaempferol, myricetin, fistein, morin
Chalcones	Lycochalcone, trans-chalcone, florentine, floridine
Flavones	apigenin, diosmin, luteolin, baicalein, chrysin,

The flavone compounds show numerous properties related mainly to their antioxidant, metal chelating and free radical neutralizing abilities. They have been shown to exert an antioxidant effect, both directly – by reduction of reactive oxygen species to more stable ones, and indirectly – inhibiting the production of free radicals [2, 3]. Anti-inflammatory, radioprotective effects have also been shown. The protective effect on the blood vessel walls is based on the inhibition of ascorbic oxidase, which reduces oxidation of vitamin C and enhances the vascular sealing effect. Additionally, anthocyanins improve visual acuity by stimulation of the ocular microcirculation [5]. Genistein and daidzein reduce the rate of cholesterol synthesis, showing the anti-atherosclerotic effects [2, 3, 5]. Flavonoids also inhibit enzymes, such as hyaluronidase and elastase, strengthening therefore the connective tissue, reducing transudates, swelling and inflammatory reactions, as well as improving the condition of the skin, delaying the aging process, and showing the analgesic effects [5]. Their anti-allergic effects are mainly based onthe inhibition of histidine decarboxylase activity [6]. An increasing number of reports indicate an antiproliferative effect of flavonoids, therefore it can be said that they can effectively inhibit tumour growth *in vitro*, and clinical studies have shown that red wine inhibits the proliferation of cells from different human cancers – such as lung, oral squamous carcinoma and prostate. In a meta-analysis for the effect of subclasses of dietary flavonoids by cancer type, flavanones were related to the upper aerodigestive tract, flavonols and anthocyanins to the colorectal, flavonols and flavones to breast cancers [7].

Effects of flavonoids on the skin. Human skin performs a number of important functions in the human body. It constitutes a protective barrier against harmful environmental stimuli, and is responsible for maintaining a proper water-electrolyte balance and constant temperature, necessary for the functioning of internal organs. Due to the presence of receptors and nerve endings, the skin is an important sensory organ that enables communication with the external world and response to various stimuli [8]. Due to the presence of immune cells, it also plays immune-related functions. The most important *SALT* (skin-associated lymphoid tissue) cells include: Langerhans cells, keratinocytes, T lymphocytes, vascular endothelial cells, macrophages, granulocytes, mast cells and melanocytes. Langerhans cells are involved in the presentation of antigens to T lymphocytes, which leads to formation of the effector lymphocytes that migrate to the target tissues and elicit a specific immune response. They are found in the basal and squamous layers of the skin, and also in small numbers in the dermis. These cells secrete cytokines, chemokines and the growth factors. They play an important role in tissue repair and in cell survival, proliferation and migration, and are the main cell population responsible for maintaining skin homeostasis through mechanisms related to stimulation and inhibition of inflammation. They are largely responsible for maintaining the integrity of the skin. The Langerhans cells lead to differentiation of T cells into Th1 (type 1 T helper) or Th2 (type 2 T helper) subclasses. As a result of antigen stimulation, they show high metabolic activity; on their surface there are receptors for the Fc fragment of IgE, tissue compatibility antigens – MHC (Major Histocompatibility Complex) class II (Human Leukocyte Antigens HLA-DR, -DQ, -DP) and MHC class I (HLA-A, B, C). They are responsible for producing tolerance or specific immune response, primarily of the cellular type and for production of CD8+ T cells, and CD4+ T cells, as well as memory lymphocytes. These cells contact keratinocytes via E cadherins, responsible for epithelial cell adhesion. Keratinocytes are the first to come into contact with pathogenic microorganisms and allergens. When stimulated, they produce multiple cytokines and induce growth and produce the immunosuppressive factors. The urocanic acid they produce in the keratinized layer of the epidermis is the main component absorbing ultraviolet radiation. After exposure to Ultraviolet B radiation (UVB), the urokaic acid in its active form, inhibits the late hypersensitivity reaction against herpes virus antigens and contact allergens. Melanocytes also produce cytokines involved in the inflammatory and immunological processes in the epidermis [9, 10].

The skin is made up of three layers: the epidermis, dermis and subcutaneous tissue. The epidermis is a thin, highly keratinised, non-vascularised outer layer, consisting of a basal layer, a spinous layer, a granular layer, a light layer, and a keratinised layer [8]. Flavonoids acting in the keratinised layer of the epidermis act as antioxidant substances and show antioxidative activity. By neutralizing free radicals, the flavonoids protect intercellular cement lipids, keratinocytes and also inhibit oxidation of vitamin C, which is essential for collagen synthesis by fibroblasts. In the deeper layers of the epidermis, they inhibit the activity of collagenase and hyaluronidase, which prevents the breakdown of collagen and hyaluronic acid, responsible for skin elasticity and hydration. The dermis is a dense, well hydrated and excellently perfused mucopolysaccharide gel with elastic properties. The papillary part is formed by a fine mesh of type I and III collagen fibers and elastic fibres, surrounded by the basal substance. The reticular layer consists of thick bundles of type I collagen fibers. The dermis also contains superficial and deep vascular plexuses, nerves, dermal cells (fibroblasts, histiocytes, mast cells, lymphocytes) and the basal substance. In this layer, flavonoids show primarily the strengthening effect on the skin microcirculation. They prevent telangiectasia and reduce fibrin synthesis, improving the blood flow. Affecting mast cells and histiocytes, they inhibit synthesis of the inflammatory mediators, and also stabilize collagen and hyaluronic acid affecting fibroblasts [1, 2, 4, 7].

Psoriasis. Psoriasis is a chronic inflammatory skin disease with a genetic and immunological basis. *LL37, β-defensins* and *S100* proteins are the most studied *AMPs* (antimicrobial peptides) associated with psoriasis, of which *LL37,* the only human *cathelicidin,* plays a pathogenic role in psoriasis. It stimulates *TLR-9 (toll-like receptor 9)* in plasmacytoid

dendritic cells (*pDCs*) and initiates the development of the psoriatic plaque in which production of type I Interferon (*IFN I)* mainly *IFN-α and IFN-β is* stimulated, which in turn promotes phenotypic maturation of myeloid dendritic cells (*mDCs*), which are involved in *Th1* and *Th17* differentiation and function, as well as *IFN-γ and* Interleukin 17 (*IL-17)* production. Activated *mDCs* migrate to the lymph nodes and secrete *TNF-α* (tumour necrosis factor α), *IL-23 and IL-12. IL-23 and IL-12* can modulate *Th17 and Th1* differentiation and proliferation, respectively. The maintenance phase of psoriatic inflammation is driven by different subsets of T cells, in which Th17 cytokines (IL-17, IL-21 and IL-22) activate keratinocyte proliferation in the epidermis. Proliferation of these cells is also stimulated by *TNF-α, IL-17 and IFN-γ;* thus, keratinocytes are directly involved in the inflammatory cascade by secreting various cytokines such as *IL-1, IL-6 and TNF-α, chemokines and AMP (antimicrobial peptides).* Abnormal and excessive keratinization of the epidermis results in the formation of characteristic lesions on the skin [11]. The primary lesion of psoriasis is a well-demarcated, reddish-brown papule with fine scaling. Initially, the lesions are small papules, of maximum 1 – 2 cm in size. They occupy extensive areas of the skin. A frequent triggering factor is infection. As the disease progresses, the lesions enlarge and become covered with silvery scales. They occur in the typical locations: knees, elbow bends and scalp. A characteristic symptom of psoriasis is *Koebner's sign,* consisting of the appearance of psoriatic lesions along the epidermal scratch line after 6 – 12 days.

Psoriasis is treated with topical preparations containing salicylic acid, urea, tar, glucocorticosteroids, and vitamin D3 derivatives. The general treatment consists of phototherapy and photochemotherapy, as well as immunosuppressive drugs, such as methotrexate and cyclosporine. Retinoids have also been used in the treatment of pustular psoriasis. Currently, the leading drugs are biologics (adalimumab, etanercept, infliximab, ustekinumab), which inhibit cytokines responsible for the development of the disease. These drugs are reserved for patients with severe and refractory psoriasis [12]. Since drugs used in psoriasis do not infrequently show some teratogenic effects and are a heavy burden to the body, there is a need for novel therapeutic solutions. There is a body of evidence that flavonoids may constitute an option. Luteolin inhibits the effect of *IL-8 and IL-6* release in epidermal keratinocytes (*NHEKs)* and cells of a non-neoplastic, immortalized human keratinocyte cell line (*HaCaT*) stimulated with *TNF-α*. Both cell lines stimulate the expression of genes that encode two different *NF-κB* subunits, encoding the *NF-κB p50 subunit* (*NFKB1)* and the *NF-κB p65 subunit,* called encoding the *v-rel reticuloendotheliosis viral oncogene homolog A* (*RELA*) subunit. Luteolin treatment of both keratinocyte cell lines reduces mRNA expression of both *NF-κB* subunits. Furthermore, luteolin reduces *HaCaT* proliferation. Additionally, luteolin (50 μM) inhibits *IFN-γ-induced* transcriptional expression of both *HSP90β and HSP90α.* The effect is closely related to the ability of luteolin to reduce the ratio of T cells (Th17/T regulatory (Treg) and Th1/Th2), and thus to alleviate psoriasis symptoms. In addition to reduction of mRNA levels, luteolin also reduces protein levels of the pro-inflammatory cytokines, *TNF-α, IL-1β, IL-6, IL-23* and *IL-17A,* and also inhibits the expression of nitric oxide synthase (iNOS) and nitric oxide (NO). Luteolin treatment is thought to have a similar effect to tacrolimus treatment [11]. Baicalein inhibits the growth of HaCaT cells which causes the cell cycle arrest in the G0/G1 phase. It does not increase the level of ROS (reactive oxygen species) or alter the integrity of the outer mitochondrial membrane; therefore, it does not activate the mitochondrial apoptotic pathway in keratinocytes. The morphological changes in keratinocytes are mainly associated with elevated *KRT10 and KRT1* expression. This process is regulated by phosphorylation of *ERK* (Extracellular Signal-Regulated Kinase), which is dependent on activation of the transient receptor potential V4 (*TRPV4*), activated by baicalein.

In conclusion, baicalein reduces keratinocyte proliferation and accelerates keratinocyte differentiation through *TRPV4* activation, which may provide an approach for the treatment of psoriasis [11]. Chrysin inhibits the stimulation of *NHEK (Normal Human Epidermal Keratinocytes)* by *IL-22, IL-17A* or *TNF- α,* and also reduces the phosphorylation of *JNK* (c-Jun N-terminal Protein Kinase)*, ERK and p38 kinase*, all components of MAPK (Mitogen-Activated Protein Kinase). In addition, it inhibits *IL-22-induced* expression of *p-STAT3* and *p-JAK2* and induction of *IκBα* (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha) by *IL-17A* or *TNF-α*. Additionally, *IL-22, IL-17A* or *TNF-α* increase the expression of chemokines, such as *CCL20 and AMPs* including *IL-37,* human defensin 2 (*hBD2),* calcium-binding protein *A9 S100 (S100A9), S100A8 and S100A7* in *NHEKs,* which is inhibited by chrysin. Chrysin reduces erythema and blood flow and increases skin surface hydration [11]. Isoflavones, such as *genistein,* and flavonoids (*kaempferol, quercetin*), as well as phenolic acids (*rosemary, caffeic, chlorogenic*), show anti-inflammatory, antioxidant, and cytostatic activities, and thus can effectively support treatment as well as prevent recurrence of the inflammatory and autoimmune skin diseases. Genistein inhibits proliferation of *TNF-α-treated HaCaT* cells, including downregulation of *MCP-1* (Monocyte Chemoattractant Protein-1), *VEGF-A* (Vascular endothelial growth factor A), *TNF-α, IL-23, IL-8 and IL-1β,* as well as inhibition of *IκBα* phosphorylation and downregulation of *NF- κB* [11]. It reduces infiltration of *CD45* inflammatory cells, as well as *Th1 cytokines* such as *TNF α, IL-6, IL-1β, and Th-17* cytokines such as *CCL2, IL-23 and IL-17.* This isoflavone also inhibits *STAT3* phosphorylation. Quercetin has anti-proliferative effects in HaCaT cells. It changes the thickness of the epidermis and reduces the thickness of the epidermal granular layer in psoriatic lesions. It exhibits the anti-inflammatory effects similar to COX (Cyclooxygenase) antagonists, such as indomethacin and COX-2 antagonists. such as celecoxib. It reduces erythema, desquamation and skin thickness. After administration of quercetin, the levels of the antioxidant markers catalase (CAT), reduced glutathione (GSH) and superoxide dismutase (SOD) are increased, and thus lipoperoxidation in psoriatic tissue is reduced. The production of the pro-inflammatory cytokines *IL-17, IL-6 and TNF-α is reduced* and the expression of the transcription factor *RelB, IKKα* and *NF-κB* inducible kinase *(NIK) is decreased*. The expression of *TNFR-related* factor *3 (TRAF3)* increases. Fisetin inhibits proliferation of *NHEKs, HaCaT and A431* cells (epidermal carcinoma cell line). It dose-dependently induces *TGase*, a marker of terminal keratinocyte differentiation, and increases the expression of *TGase-1, filaggrin, caspase-14, KRT10* and *KRT10* differentiation markers. This flavonoid also increases

the nuclear expression of *AP-1* members (a transcription factor that plays an important role in regulating keratinocyte differentiation, terminal differentiation, cytokine production and inflammation). Fisetin-treated NHEKs inhibit *IL-22-induced* proliferation through the P13K/Akt/mammalian Target of Rapamycin (*mTOR*) signaling pathway, as well as *TNF-α-induced* activation of *MAPK and P13K/Akt/mTOR* signaling pathways. Secretion of *TNF-α, IL-1β, IL-1α, IL-8, IL-6* and the profibrotic mediator TGF-α is also reduced by fisetin. Furthermore, in peripheral blood mononuclear cells (*PBMCs*), it inhibits *mRNA* accumulation of *IL-17A and IFN-γ*. Fisetin inhibits proliferation and induction of expression of the differentiation markers *desmoglein-1, TGase-1, filaggrin, involucrin and KRT10* in the squamous and granular layers of epidermal cells and inhibits the expression of *IL-17A*, *phospho-p70* kinase ribosomal protein *S6 (p-p70S6K)* and psoriasis markers associated with activation of the *mTOR* pathway [13]. Kaempferol inhibits T cell proliferation, phosphorylation of *p70S6K* downstream of *mTOR* signaling. Causes smoothing of the epidermis and reduction of parakeratosis. It reduces *CD3+ T-cell* infiltration in the lesional skin. Furthermore, this flavonoid increases the frequency of *CD4+FoxP3+Treg* cells and the expression of IL- and FoxP3 genes. On the other hand, kemferol decreases the percentage of *IL-17A+CD4+ or RORγt+CD4+ T* cells and the *mRNA* expression of *TNF-α, IL-6 and IL-17A*. Both quercetin and kaempferol reduce psoriasis symptoms through their antioxidant properties and regulation of the expression of key molecules in psoriasis, as well as through modulation of inflammation. Fisetin has shown various properties related to inhibition of cell growth as well as the signaling and inflammatory profile of various cell lines [11].

In the phytotherapy of autoimmune diseases, including psoriasis, red clover is often used in combination with other plants, such as burdock and curly sorrel. These plants inhibit the autoimmune processes, stimulate wound healing and inhibit epidermal cell division. A decoction of fresh leaves of *Olax scandens Roxb*., also rich in flavonoids and phenolic compounds, is often given as a beverage to psoriatic patients at a dose of 20 ml for 20 days with good results. A paste made from the leaves of *Pedalium murex L* containing *flavonoids, phytosterols, triterpenes* can be used as a treatment for the affected skin. Flavonoids show documented immunomodulatory, soothing and anti-inflammatory effects, making them well suited for the treatment of psoriasis [14].

Acne vulgaris. Acne vulgaris is one of the most frequent skin diseases. Its main cause, associated with hormonal changes, is oversecretion of sebum, leading to the blockage of sebaceous gland ducts, which then effects the formation of blackheads. Bacteria of the *Cutibacterium acnes* species, multiplying in blackheads, lead to formation of inflammation. The genetic background, consumption of certain foods and drinks, stress, use of tobacco and damage or other skin diseases may also play a role in the formation of acne. Acne lesions usually consist of non-inflammatory closed comedones, open comedones, and inflammatory papules, nodules, pustules or cysts, usually occurring on the face, chest or upper back. The highest incidence occurs during adolescence.

Topical treatments include benzoyl peroxide, azelaic acid, retinoids and antibiotics. These are drugs with a soothing, antibacterial and anti-inflammatory effect. If the topical treatment does not have a curative effect, general treatment with isotretinoin, antibiotics, hormonal therapy or steroid therapy should be applied [12]. These medications often cause multiple side-effects, necessitating close monitoring of the patient's condition during therapy. In support of the treatment of this disorder, preparations of *Centella Asiatica,* rich in *quercetin* and *kaempferol,* are used. They may be administered orally and in the form of subcutaneous or intramuscular injections. They exhibit potent antimicrobial and anti-inflammatory effects similar to *COX-2* antagonists. They cause reduction in the inflammatory proteins, *IL-17, IL-6 and TNF-α,* as well as decrease in the expression of *NF-κB* inducible kinase *(NIK). Rosemary* containing *luteolin, genquanin, diosmethine,* shows strong antiseptic, bactericidal effects on streptococci and staphylococci. It reduces the pro-inflammatory cytokines *TNF-α, IL-1β, IL-6, IL-23 and IL-17A, IL-6, and* inhibits the expression of iNOS and NO, thus significantly reducing inflammation and telangiectasias. In skin disorders it is used in the form of compresses. It is used in the treatment and care of oily and polluted skin. *Common nettle* rich in *quercetin, rutin* and *kaempferol* is used as an external compress in case of seborrhea and inflammation [1, 15, 16]. By combining the above natural therapies, very good therapeutic effect can be achieved with less strain on the body.

Rosacea. Acne rosacea is a chronic, inflammatory skin disease affecting the midface, of which the most common form is telangiectatic- erythematous, characterized by transient, paroxysmal reddening of the skin associated with vascular hyperreactivity. The persistent lesions may have the character of diffuse erythema or telangiectasias, accompanied by a burning sensation of the skin. After erythema and telangiectasias, papules and pustules appear on the skin. Hypertrophy and fibrosis of the sebaceous glands may also occur leading to limited hypertrophy (*rhinophyma)*. Topical treatment includes metronidazole 0.75% and 1%, azelaic acid for inflammatory lesions, 10% sodium sulfacetamide with 5% sulfur, benzoyl peroxide and macrolides. The general treatment includes tetracyclines, macrolides, isotretinoin, *H.pylori* eradication and the surgical procedures [12].

Not only chemicals in the form of the above-mentioned drugs are effective in the treatment of rosacea. *Lycochalcone* is a natural flavonoid extracted from licorice root. It exhibits antibacterial, antiparasitic, anticancer and immunomodulatory effects. The mechanism of action is based on disruption of energy metabolism, similar to antibiotics that inhibit microbial respiration. Used in topical preparations it shows anti-inflammatory effects and reduces irritation and erythema. Systematic application of liquivalcon creams increases the level of epidermis moisturizing, improves the skin barrier function, reduces the intensity of erythema, as well as dryness, itching and burning of the skin. Licochalcone creams in daily care of skin affected by rosacea can bring very good therapeutic results [17].

Atopic dermatitis. Atopic dermatitis (AD) is a chronic inflammatory skin disease, accompanied by persistent itching. Pathogenesis of this disease is complex and multifactorial. It consists of genetic and immunological disorders, defect of the epidermal-dermal barrier function resulting from mutations in genes coding proteins in the epidermis and serving to maintain its integrity, e.g. the filaggrin gene (*FLG)* or the serine peptidase inhibitor Kazal type 5 gene (*SPINK5*) and the immune system, i.e. mutations

in the gene for interleukin 4, its receptor, interleukin 13 or chemokine *RANTES*. Interleukins *IL-4* and *IL-13* produced following activation of *Th2* are overexpressed and induce immunoglobulin E (IgE) production in AD patients [18]. Keratinocytes produce *involucrin, loricrin* and *filaggrin,* which bind keratin fibres and form the keratinised cell envelope. In addition, hyaluronic acid is synthesized in the keratinocytes and is responsible for proper hydration of the skin. Aquaporins *(AQPs)* are small hydrophobic integral membrane proteins that regulate the rate of water retention in the skin and other organs. To date, 13 types of *AQPs* have been identified in mammals, of which *AQP3* is involved in water and glycerol transport and is expressed on keratinocyte membranes. Keratinocytes also produce antimicrobial peptides such as defensin *(β-defensin (HBD)-1, HBD-2, HBD-3), cathelicidin, secretory leukocyte protease inhibitor, dermcidin and adrenomedullin,* which serve to defend against infectious agents. Abnormalities of these skin cell components and antimicrobial peptides, together with genetic and environmental factors and imbalances in the immune response, are the main causes of AD [18]. The clinical picture consists of eczematous lesions with age-specific localisation. A recurrent course with consecutive periods of exacerbation and remission is characteristic.

The treatment of AD is long and laborious. Preparations are used to restore the hydrolipidic skin barrier. Emollients, glucocorticosteroids, antibiotics, fungicides, ointments with urea or salicylic acid are used. The use of tacrolimus or pimecrolimus with immunosuppressive effects has good results. It is important to ensure that the patient does not scratch. Antihistamines such as hydroxyzine will have a supportive effect in pruritus [6, 9, 12]. Baicalein reduces skin eczema caused by contact allergy to 2,4-dinitrofluorobenzene (*DNFB*). It induces epidermal differentiation through induction of keratinocyte differentiation. The anti-inflammatory effect of baicalein reduces tissue swelling, inflammatory cell infiltration in the skin, redness, desquamation and skin thickness, and attenuates the inflammatory response. Baicalein treatment reduces the expression of *TNF-α, IL-23, IL-22 and IL-17A* and the number of dermal γδT cells associated with the production of TNF-α, IL-22 and IL-17 [11]. *Rhealba* oat young shoot extract rich in *C-glycosylflavones, tricin-type flavones* and *flavonolignans* has been shown to have antipruritic, anti-inflammatory, irritant-soothing and wound-healing properties. It has found application in the treatment of patients with AD. Its action is due to inhibition of cyclooxygenase, regulation of Th1 and Th2 lymphocyte production and alteration of dendritic cell phenotype and function. Extracted from barley germ (*Hordeum vulgare L.),* apigenin significantly induces the expression of genes and proteins (*filaggrin, loricrin, AQP3, HA, HAS-1, HAS-2 and HAS-3*) in HaCaT cells, which play an important role in maintaining the physical barrier and water retention in the skin. It increases the expression of antimicrobial peptides (*HBD-1, HBD-2, HBD-3 and LL-37)*, which play an important role in acting as a chemical barrier to HaCaT cells. Unfortunately, it has very low solubility in water, so delivery systems need to be developed to improve absorption and bioavailability, nevertheless it is a very good candidate for the relief of AD symptoms [18]. Many other plants rich in quercetin, myricetin, rutoside and kaempferol are also used supportively in the treatment of this condition [19]. They are used in the production of modern emollients, so-called *emollients plus,* which are enriched with flavonoids, saponins or bacterial extracts / lysates. As a result, in addition to their standard action, they restore the microbiological balance, exert some anti-inflammatory, anti-pruritic and immunomodulatory effects. Although of plant origin, they do not contain proteins that could lead to the development of allergies [9].

Allergic urticaria. Allergic urticaria is a disease in which an IgE-mediated reaction and histamine release from mast cells occurs following exposure to a trigger agent. The association between *HLA DRB1*04* (encoding DR4) and the associated *DQB1*0302* allele (encoding DQ8) has been found in patients with urticaria. The HLA region is associated with most autoimmune diseases. In addition to urticaria*, HLA-DR4* is also associated with rheumatoid arthritis and other autoimmune blistering diseases. Significant associations have been found between *TGF-β1* gene promoter polymorphisms in urticaria and high affinity promoter of the IgE receptor alpha subunit (*FcεRIα*) and chronic hypersensitivity to anti-inflammatory drugs [20,21]. Mast cells and basophils mediate allergic reactions through secretion of β-hexosaminidase. *IgE* binds to the IgE-binding subunit of the high affinity IgE receptor (*FcεRI*), a heterotetrameric receptor on mast cells and basophils, and stimulates degranulation and cytokine secretion, leading to an allergic reaction [18]. Binding of IgE to the α subunit results in activation of the β and γ subunits of *FcεRI*, with consequent recruitment of *Lyn* and *Syk* and induction of protein tyrosine kinase (*PTK*) phosphorylation. Activated *Syk* is involved in phosphorylation and activation of phospholipase C (*PLC*)-γ. Mitogen-activated protein kinases (*MAPKs*) such as extracellular signal-regulated kinase (*ERK*), c-Jun N-terminal protein kinase (*JNK*) and *p38* are also activated by *FcεRI-IgE* binding. Phosphorylation and activation of these kinases mediate expression of the tumor necrosis factor-α (*TNF-α*) and *IL-2*. Macrophages play an important role in the immune response and regulate various inflammatory mediators, such as NO, prostaglandins (*PG*) and anti-inflammatory cytokines. NO is mainly produced by iNOS and promotes the inflammatory response inducing the expression of the inflammatory mediators. Cyclooxygenase (*COX*), is an enzyme that converts arachidonic acid to PG. COX-2 is mainly expressed during the inflammatory response and induces production of prostaglandin E2 (*PGE2*), an inflammatory mediator associated with pain and fever. In addition, *TNF-α*, plays an important role in induction of the inflammatory responses by activating T lymphocytes and macrophages and enhancing the effect of other pro-inflammatory cytokines, leading to the inflammatory response. *IL-6* is also an important inflammatory factor secreted by macrophages after exposure to *LPS (lipopolysaccharides)* [18]. The primary lesion in urticaria is an urticarial wheal surrounded by redness, causing severe itching and burning of the skin. The lesions are non-painful and resolve without leaving scars or skin discolouration. The lesions may be accompanied by angioedoema of the subcutaneous tissues with a stronger intensity on one side of the body. The skin is often reddened. Red dermographism is observed in patients.

Urticaria is divided into acute urticaria (up to 6 weeks) and chronic urticaria (over 6 weeks). Apart from allergy, urticaria may be triggered by drugs, physical factors such as cold, pressure or sunlight, as well as infections, tumours,

autoimmune diseases. The mainstays of treatment are antihistamines, glucocorticosteroid, and antileukotrienes [12, 22, 23]. It seems that *quercetin,* present in honey, red grapes and red wine, among others, can be a good support of therapy. Apart from its applications similar to *COX and COX-2* antagonists and reduction of lipoperoxidation in adipose tissue, most importantly, it reduces levels of the pro-inflammatory cytokines *IL-17, IL-6 and TNF-α.* It inhibits production and release of histamine, an allergic and inflammatory substance and stabilizes the cell membrane of mast cells. Quercetin decreases the secretion of tryptase and interleukin-6 (IL-6). In addition, it negatively regulates histidine decarboxylase (HDC) mRNA from human mast cells (HMC)-1, making it a natural inhibitor of mast cell secretion and preventing the development of an allergic reaction and thus the development of urticaria [16]. In addition, *apigenin* effectively inhibits NO production and cytokine expression *(IL-1β, IL6, COX-2 and iNOS),* as well as *ERK and JNK* phosphorylation associated with the *MAPK* signaling pathway in *RAW264.7* cells. It also inhibits the expression of cytokines *(TNF-α, IL-4, IL-5, IL-6, IL-13 and COX-2)* and *FcεRIα/γ, as well as the* phosphorylation of signaling molecules *(Lyn, Syk, PLCγ1, ERK and JNK)* corresponding to the allergic response pathway in *RBL-2H3 cells.* Thanks to such properties, it alleviates inflammation and reduces the manifestations of urticaria induced by an allergic reaction [18].

Mycosis. The skin and the mucous membrane mycoses belong to the group of infectious diseases caused by dermatophytes, yeast-like fungi – *Candida albicans* and *Malassezia furfur.* and molds. Dermatophytes cause the mycoses proper. Moulds cause systemic infections affecting mostly the internal organs. *Candida albicans* is responsible for candidiasis of the mucous membranes, nails and skin burns. Dandruff is caused by the yeast *Malassezia furfur.* Tinea capitis manifests as erythematous-edematous lesions with papules and pustules on the periphery or erythematous-exfoliative foci with inflammatory reaction. In addition, thinning, and even truncation of hair in the area of skin lesions, is characteristic. The changes are often accompanied by maceration of the epidermis. After some time, the wound may start to ooze secretion and produce an unpleasant smell. Tinea is frequently accompanied by intense itching, redness, irritation, cracking of the skin and peeling of the epidermis. The nail plate affected by mycosis undergoes thickening and discoloration; it becomes brittle and excessively calloused and dirty. Most often infected are the skin between toes, feet, soles and palms.

The treatment of mycosis is long-lasting and therefore requires patience and discipline of the patient. It includes the use of external preparations, oral medications, disinfection of shoes and underwear, and observance of the preventive measures. The most common drugs used in mycosis are: *terbinafine, itraconazole, fluconazole, miconazole* [12, 24]. Modern preparations use flavonoids and chalcones derived from *Inula viscose Ait.* and *Zuccagnia punctata Cav.* They show significant antifungal activity against dermatophytes, even at low concentrations. *Quercetin* and *trans-chalcone* inhibit the biosynthesis of essential fungal cell wall components and block fatty acid synthase (*FAS*) in yeast and mycobacterial cells by down-regulating the expression of the relevant genes. Also used in acne, *licochalcone* is used in the prevention and treatment of mycosis fungoides by slowing the growth of mycobacteria when interacting with the keratinocyte cell line [24].

Ulcers, sores, burns, skin wounds. Secondary skin lesions, such as ulcers, represent open wounds that are difficult to heal. Their management requires a holistic approach to the patient. Preparations to stimulate the circulatory system, including acetylsalicylic acid and diuretics are often used. In case of an accompanying bacterial infection, antibiotics are used. The wounds often require surgical treatment. Local treatment includes disinfectants, absorptive dressings, hydrogel dressings and dressings with silver salts. The skin around the wound should be lubricated with emollients or cholesterol ointment [12]. Plants rich in *apigenin, kaempferol* and *quercetin work* very well as dressings to support wound healing, many of them being as poultices [1, 2, 25]. One of the many sources rich in these flavonoids is *honey.* Added to a dressing and applied to wounds, it has antimicrobial, anti-inflammatory and analgesic effects, cleanses them of dead tissue, stimulates granulation, accelerates epithelialization and enhances the scarring process. In addition, honey does not irritate wounds and protects them from repeated microbial infection [26]. Green tea extract, rich in *epicatechin gallate*, is also used in the treatment of skin wounds. It exhibits the anti-inflammatory, antibacterial and antioxidant effects, and has beneficial effects on healing and scar formation in terms of stimulation of angiogenesis. It was observed to increase VEGF expression by affecting the activity of the enzymes, the nitric oxide synthase (NOS) and cyclooxygenase. *In vitro* studies indicate a higher maturity of collagen fibers and a compact fiber arrangement in scars [16].

SUMMARY

Flavonoids are the largest group of polyphenols present in plant raw materials. The flavonoid compounds are considered to be among the most important biologically-active compounds of plant origin. Plants rich in flavonoids have a multitude of desirable actions that can not only prevent the development of disease, but also treat it effectively. The antioxidant and photoprotective activities of flavonoids are the main factors influencing their preventive use in the development of skin diseases. Thanks to these two applications, the risk of tumour formation is significantly reduced. The anti-allergic effect reduces the risk of developing atopic dermatitis. Due to their circulation-stimulating properties, they accelerate the healing of long-lasting wounds and ulcers. Plants rich in flavonoids can be used as dressings and poultices. Their extracts can be added to creams, solutions. An increase in the diet of fruit and vegetables, which are sources of these biologically active substances, may be a significant factor in preventing the development of the disease, as well as supporting the healing process. It is worth conducting research on plant raw materials, as they can be a valuable material, rich in therapeutic substances.

Table 2. Activities of flavonoids [2, 4, 5, 23, 27, 28]

Source	Flavonoids	Action	Molecular Mechanism
Blueberries *Vaccinium myrtillus L.*	Cyanidine, delphinidin, pelargonidin, peonidin, malvidin, petunidin, myristilin	Keranocyte-stimulating, regenerating, skin-tightening and moisturising effects, antiseptic effects, whitening of pigmentation, sealing and vascular elasticity.	Targeting mitogen-activated protein kinase (MAPK) pathway and activator protein 1 (AP-1) factor, targeting nuclear factor *kappa* B (NF-*κ*B) pathway and *cyclooxygenase* 2 (*COX*-2) gene, c-Jun NH2-terminal kinase (JNK)-mediated caspase activation.
Red grapes, red wine *Vitis vinifera L.*	Quercetin, catechin, epigallocatechin, myricetin, tannin, anthocyanins, flavones, catecholamines, resveratrol	Antioxidant, antiseptic, antiviral, vascular sealing and elasticity effects	Scavenging of hydroxyl radical (OH-), hydrogen peroxide (H2O2), and superoxide anion (O2-). Decreasing the secretion of tryptase and interleukin-6. Negative regulation of histidine decarboxylase (HDC) mRNA from human mast cells (HMC)-1.
Vine fruit *Vitis vinifera L.*	Flavone oligomers, anthocyanins	Anti-hyaluron action, collagen maturation, protection of blood vessels, preservation of connective tissue cohesion	Inhibition of nuclear factor kappa-B (NF-κB). Inhibition of phosphorylation of p38 and c-Jun N-terminal kinases.
Ginseng *Panax ginseng*	Kemferol, trifolia, panasenoside, quercetin, rutin, saponins	Immunostimulating effect, moisturising, regenerating, stimulating skin metabolism, slowing down keratinisation, stimulating circulation in the vessels of the dermis	Stimulates NO, blocks C-Jun N-terminal kinase, inhibits TNF-α-induced phosphorylation of MKK4, and activates the JNK-AP-1 pathway.
Green tea *Camellia sinensis*	(-)Epigallocatechin gallate, catechin gallate, epigallocatechin, epicatechin, tannin	Antioxidant, anti-inflammatory, anticancer, photoprotective, antibacterial, regenerative effects	Increasing VEGF expression by affecting the activity of the enzymes, the nitric oxide synthase (NOS) and cyclooxygenase
Ginkgo leaves *Ginkgo bilobae folium*	Rutin, quercetin, kemferol, ginkgolides, isoginkgetin, bilobalide	Blood circulation-stimulating, photoprotective, antioxidant effect,	Regulation of different cellular signaling pathways such as Wnt/β-catenin, p53-independent pathway, PI3K/Akt, JAK/STAT, MAPK, p53, apoptosis as well as NF-κB signaling pathways
Lime blossom *Inflorescentia Tiliae*	Quercetin, rutin, catechol tannins, phloroglucinol	Moisturising, emollient, antioxidant, anti-inflammatory, anti-hypertensive action,	Reduction in the inflammatory proteins, *IL-17, IL-6 and TNF-α,* decreases expression of *NF-κB* inducible kinase *(NIK)*
Rosemary *Rosmarinus L*	Luteolin, genquanin, diosmetin, phenolic acid, rosemary acid	Analgesic, anti-inflammatory, anti-allergic, antioxidant, vascular sealing, anticancer, photoprotective, antimicrobial effects.	Inhibition of *IFN-γ-induced* transcriptional expression of *HSP90β and HSP90α.* Reduction of the ratio of T cells (Th17/T regulatory (Treg) and Th1/Th2). Reduction of protein levels of the pro-inflammatory cytokines *TNF-α, IL-1β, IL-6, IL-23 and IL-17A.* Inhibition of the expression of nitric oxide synthase (iNOS) and nitric oxide (NO)
Świetlik *Euphrasia*	Apigenin, chrysoeriol, rutoside, kemferol, quercetin and luteolin derivatives, tannins, phenolic acids	Anti-inflammatory, antioxidant, antibacterial, astringent, toning, soothing, anti-allergenic, reduction of vascular permeability	Inhibits NO production, cytokine expression *(IL-1β, IL6, COX-2 and iNOS), ERK and JNK* phosphorylation associated with the *MAPK* signaling pathway in *RAW264.7* cells. Inhibits the expression of cytokines *(TNF-α, IL-4, IL-5, IL-6, IL-13 and COX-2)* and *FcεRIα/γ,* phosphorylation of signaling molecules *(Lyn, Syk, PLCγ1, ERK and JNK)*
Pomegranate *Punica granatum L.*	Delphinidin, pelargonidin, cyanidin, ellagic and gallic acid, ellagotannins and proanthocyanidins	Antioxidant effect, soothing, stimulating collagen and elastin synthesis	Targeting nuclear factor *kappa* B (NF-κB) pathway and *cyclooxygenase* 2 (*COX*-2) gene, c-Jun NH2-terminal kinase (JNK)-mediated caspase activation.
Strawberry *Fragaria grandiflora*	Anthocyanins, catechins, quercetin, kemferol, resveratrol	Purifying, photoprotective, soothing, anti-acne, pore tightening, moisturising action,	Inhibits T cell proliferation, phosphorylation of *p70S6K* downstream of *mTOR* signaling.
Honey *Mellis*	Quercetin, hesperidin, kemferol, myricetin, luteolin, apigenin	Antimicrobial, anti-inflammatory, pain relieving, cleansing wounds of dead tissue, deodorising, stimulating granulation, accelerating epithelization, enhancing the scarring process.	Reduces levels of the pro-inflammatory cytokines *IL-17, IL-6 and TNF-α.* Inhibits production and release of histamine, an allergic and inflammatory substance and stabilizes the cell membrane of mast cells. Decreases the secretion of tryptase and interleukin-6 (IL-6). Negative regulation of histidine decarboxylase (HDC) mRNA from human mast cells (HMC)-1

Table 3. The role of flavonoids in selected skin diseases

Flavonoid	Disease	Mechanism	References
Luteolin	Psoriasis	Reduces ratio of T cells (Th17/T regulatory (Treg) and Th1/Th2), reduces mRNA levels, reduces protein levels of the pro-inflammatory cytokines, *TNF-α, IL-1β, IL-6, IL-23, IL-17A,* inhibits the expression of nitric oxide synthase (iNOS) and nitric oxide (NO).	[11]
	Acne Vulgaris	Reduces pro-inflammatory cytokines *TNF-α, IL-1β, IL-6, IL-23 and IL-17A, IL-6, and* inhibits expression of iNOS and NO.	[16]
Baicalein	Psoriasis	Inhibits growth of HaCaT cells which causes cell cycle arrest in the G0/G1 phase. Reduces keratinocyte proliferation and accelerates keratinocyte differentiation through *TRPV4* activation.	[11]
	Atopic Dermatitis	Reduces expression of *TNF-α, IL-23, IL-22 and IL-17A* and number of dermal γδT cells associated with the production of TNF-α, IL-22 and IL-17.	[11]
Chrysin	Psoriasis	Inhibits stimulation of *NHEK* by *IL-22, IL-17A* or *TNF- α*. Reduces phosphorylation of *JNK, ERK and p38 kinase*.	[11]
Genistein	Psoriasis	Inhibits proliferation of *TNF-α-treated HaCaT* cells, *MCP-1* , *VEGF-A, TNF-α, IL-23, IL-8 and IL-1β*. Inhibits *IκBα* phosphorylation and downregulation of *NF- κB*.	[11]
Quercetin	Psoriasis	Has anti-proliferative effects in HaCaT cells.	[11]
	Acne Vulgaris	Reduction in inflammatory proteins, *IL-17, IL-6 and TNF-α,* as well as decrease in the expression of *NF-κB* inducible kinase *(NIK)*.	[15]
	Allergic urticaria	Applications similar to *COX and COX-2* antagonists, reduction of lipoperoxidation in adipose tissue, reduction of levels of the pro-inflammatory cytokines *IL-17, IL-6 and TNF-α*. Inhibition of production and release of histamine. Decreases the secretion of tryptase and interleukin-6 (IL-6).	[16]
Fisetin	Psoriasis	Inhibits proliferation of *NHEKs, HaCaT and A431* cells. Inhibits *IL-22-induced* proliferation through the *mTOR* signaling pathway, as well as *TNF-α-induced* activation of *MAPK and P13K/Akt/mTOR* signaling pathways.	[13]
Kaempferol	Psoriasis	Inhibits T cell proliferation, phosphorylation of *p70S6K* downstream of *mTOR* signaling.	[11]
	Acne Vulgaris	Reduction in inflammatory proteins, *IL-17, IL-6 and TNF-α,* as well as decrease in the expression of *NF-κB* inducible kinase *(NIK)*.	[15]
Lycochalkone	Rosacea	Exhibits antibacterial, antiparasitic, anticancer and immunomodulatory effects. The mechanism of action is based on disruption of energy metabolism, similarly to antibiotics that inhibit microbial respiration.	[17]
Apigenin	Atopic dermatitis	Induces expression of genes and proteins (*filaggrin, loricrin, AQP3, HA, HAS-1, HAS-2 and HAS-3*) in HaCaT cells. Increases expression of antimicrobial peptides (*HBD-1, HBD-2, HBD-3 and LL-37)*.	[18]
	Allergic urtricaria	Inhibits NO production and cytokine expression *(IL-1β, IL6, COX-2 and iNOS),* as well as *ERK and JNK* phosphorylation associated with the *MAPK* signaling pathway in *RAW264.7* cells.	[18]
Trans-chalcone	Mycosis	Inhibits biosynthesis of essential fungal cell wall components and block fatty acid synthase (*FAS*) in yeast and mycobacterial cells by down-regulating the expression of the relevant genes.	[24]
Epicatechin Gallate	Ulcers, sores, burns, skin wounds	Increases VEGF expression by affecting the activity of the enzymes, the nitric oxide synthase (NOS) and cyclooxygenase	[16]

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