Received: 5 November 2020 | Accepted: 2 December 2020

DOI: 10.1002/biof.1699

REVIEW ARTICLE

Biofactors WILEY

Luteolin as a modulator of skin aging and inflammation

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Abstract

Luteolin belongs to the group of flavonoids and can be found in flowers, herbs, vegetables and spices. It plays an important role in defending plants, for example against UV radiation by partially absorbing UVA and UVB radiation. Thus, luteolin can also decrease adverse photobiological effects in the skin by acting as a first line of defense. Furthermore, anti-oxidative and anti-inflammatory activities of luteolin were described on keratinocytes and fibroblasts as well as on several immune cells (e.g., macrophages, mast cell, neutrophils, dendritic cells and T cells). Luteolin can suppress proinflammatory mediators (e.g., IL-1β, IL-6, IL-8, IL-17, IL-22, TNF-α and COX-2) and regulate various signaling pathway (e.g., the NF-κB, JAK–STAT as well as TLR signaling pathway). In this way, luteolin modulates many inflammatory processes of the skin. The present review summarizes the recent in vitro and in vivo research on luteolin in the field of skin aging and skin cancer, wound healing as well as inflammatory skin diseases, including psoriasis, contact dermatitis and atopic dermatitis. In conclusion, luteolin might be a promising molecule for the development of topic formulations and systemic agents against inflammatory skin diseases.

KEYWORDS

inflammation, luteolin, reactive oxygen species, skin

1 | INTRODUCTION

Luteolin is a secondary plant metabolite that belongs to the group of flavonoids (Figure 1). Flavonoids are polyphenols characterized by a diphenylpropanstructure (C6–C3–C6) and play an important role in defending plant cells against UV radiation or in the attraction of pollinators and seed dispersers.[1,2] Luteolin is widely

Abbreviations: ACD, Allergic contact dermatitis; AMP, Antimicrobial peptides; AP-1, Activator protein 1; CHS, Contact hypersensitivity; CPD, Cylobutane pyrimidine dimers; COX-2, Cytochrome c oxidase subunit II; CREB, Cyclic AMP response element binding protein; DC, Dendritic cells; ECM, Extracellular matrix; EGF, Epidermal growth factor; EMT, Epithelial-mesenchymal transition; ERK, Extracellular signal-regulated kinase; ESCD, European Society for Contact Dermatitis; GM-CSF, Granulocyte macrophage-colony stimulating factor; HA, Hyaluronic acid; HDM, House dust mite; ICD, Irritative contact dermatitis; iNOS, Inducible nitric oxide synthases; JAK-STAT, Janus kinases (JAKs), signal transducer and activator of transcription proteins (STAT); LUT-7G, Luteolin-7-glucoside; MAPK, Mitogen-activated protein kinase; MED, Minimal erythema dose; MMP, Matrix metalloproteinases; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NO, Nitric oxide; NET, Neutrophil extracellular traps; PGE2, Prostaglandin E2; PGD2, Prostaglandin D2; ROS, Reactive oxygene species; RPS19, the ribosomal protein S-19; TLR, Toll-like receptor; TNF-α, Tumor necrosis factor α; UVB, Ultra violet B; VEGF, Vascular endothelial growth factor.

[Correction added on 13 January 2021, after first online publication: Projekt Deal funding statement has been added.]

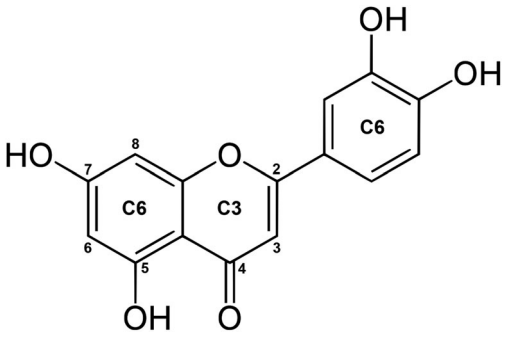

FIGURE 1 Structural formula of luteolin

distributed in flowers (*Reseda luteola* and Chrysanthemums), herbs (e.g., parsley, peppermint, oregano and thyme), vegetables (e.g., celery seeds, sweet bell peppers, carrots and broccoli) and spices (cardamom and anise).[3,4] However, compared to other secondary plant substances, luteolin is only a minor component in our daily nutrition (less than 1 mg/day).[5] In plants, luteolin mostly occurs in the form of glycosides that are cleaved after nutritional uptake. The aglycones are then conjugated and metabolized, which has to be considered when evaluating in vitro studies. Some data for the oral and topical bioavailability of luteolin and its glycosides exist, but more studies are needed to evaluate the physiological and therapeutical potential of luteolin.

Luteolin, like other flavonoids, is a pleiotropic substance so that its pharmacological impact may not be explained by a single biochemical effect. The anti-inflammatory activities of luteolin are displayed at micromolar concentrations and include suppression of proinflammatory mediators (e.g., COX-2, NO, IL-6, IL-1β, TNF-α) and the regulation of several signaling pathways, including the NF-κB, AP-1 and JAK–STAT pathway. All these pathways are connected via crosstalk and luteolin can regulate and inhibit these signal transduction pathways.[6] However, the most important effect of luteolin consists of its potent anti-oxidative power with excellent radical scavenging and cytoprotective properties.[7,8] Therefore, the anti-inflammatory effects of luteolin may be attributed in part to its anti-oxidative capacities. This is especially important as oxidative stress plays a tremendous role in many inflammatory processes of the skin (e.g., radiation-induced erythema and skin cancer,[9,10] psoriasis,[11] wound healing[12] and contact dermatitis[13]). Furthermore, luteolin interacts with other anti-oxidants such as vitamins and cellular redox systems. In this way, luteolin can synergistically augment its anti-oxidative power.[14] While some flavonoids like quercetin, genistein and catechins showed some pro-oxidative activity in H_2O_2–generating systems or after metabolic activation, luteolin was described as safe.[15]

In this review, we will outline the effect of luteolin on various skin diseases, including skin aging and skin cancer, wound healing, psoriasis, contact dermatitis and atopic dermatitis.

2 | SKIN AGING AND SKIN CANCER

Solar ultraviolet (UV) radiation leads to various immediate and long-term deleterious effects, including acute erythema (sunburn), degradation of collagen and elastin and wrinkled appearance of the skin (photoaging). Short wave ultraviolet B (UVB) radiation leads already within 24 h of exposure to skin damage characterized by sunburn cell formation,[16] induction of cyclobutane pyrimidine dimers (CPD), oxidative damage of cellular components such as lipid membranes, mitochondria, DNA and proteins[17] and an acute inflammatory response.[18] At least 50% of UVB-induced damage is attributable to the formation of reactive oxygen species (ROS). ROS are generated by transferring electromagnetic energy from UVB radiation to molecular oxygen. Increased generation of hydrogen peroxide can be observed in vivo already 10 min after UVB irradiation with twofold of the minimal erythema dose (MED).[19] To cope with the deleterious effects of UV radiation, biological systems have developed various protective molecules such as the UV-absorbing melanin, carotenoids, retinoids, the vitamins ascorbic acid and tocopherol[20] and proteins involved in DNA repair and detoxification of ROS.[17] However, this endogenous protective system may collapse when exposed to prolonged and repeated UV radiation. UVB-induced skin damage may be prevented by avoidance of intense sun exposure, use of sunscreens and topical and systemic administration of anti-oxidants to reduce free radical production.[19,21] Two structural features of luteolin are responsible for its strong anti-oxidative power. The presence of a C2–C3 double bond that donate a hydrogen/electron and stabilizes in this way the radical species and the oxo group at C4 (Figure 1) that binds transitional metal ions such as iron and copper to prevent oxidative damage through the Fenton reaction, inhibit pro-oxidant enzymes and induce antioxidant enzymes. This is important because ROS production contributes to the activation of mitogen-activated protein kinase (MAPK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and downstream regulation of NF-κB-dependent genes such as cyclooxygenase 2 (COX-2).[19,22] COX-2 plays a key role in acute UVB-induced inflammation by catalyzing the generation of prostaglandin E_2 (PGE_2) from prostanoid precursors.[23] In addition, COX-2 overexpression in chronically sun-exposed skin seemed to be associated with the development of non-melanoma skin cancer (actinic keratoses, squamous cell carcinoma, basal cell carcinoma).[24,25] Luteolin inhibited

both UVB-induced COX-2 expression and PGE_2 synthesis.[26] We could show that these effects, at least in part, were mediated by interference with the MAPK signaling pathway.[26] Furthermore, the COX-2 promotor contains multiple binding sites for transcription factors, including AP-1, NF-κB and the cyclic AMP response element binding protein (CREB) that are induced by UV irradiation.[27] In comparison to established anti-oxidants such as trolox and N-acetyl cysteine, luteolin not only reduced UVB-induced oxidative stress but it also displayed cytoprotective effects in H_2O_2-treated cells at low concentrations and attenuated UVB-induced nitrative stress.[26]

Furthermore, luteolin can absorb UV radiation and reduce UV transmission.[26] The resulting reduction of photons reaching the epidermis represents a first line of defense. Luteolin prevented UVB-induced CPD formation in vitro and in vivo.[26] CPD formation in the skin may lead to mutations of p53 contributing to the development of nonmelanoma skin cancer.[21,28] UVB exposure functions as complete carcinogen, because it is capable of triggering the initiation, promotion and progression of carcinogenesis.[27] About 90% of nonmelanoma skin cancer and 65% of melanomas are attributable to UVB.[27] In this context it is remarkable that luteolin was able to inhibit cell proliferation, induce apoptotic cell death and cause cell cycle arrest in the human melanoma cell line A375.[29] Intraperitoneally injected luteolin reduced the tumor growth of A375 cells in vivo in a mouse xenografts model and decreased matrix metallopeptidase 2 (MMP -2) and matrix metallopeptidase 9 (MMP-9) expression via the phosphatidyl inositol 3-kinase/protein kinase B (PI3K/Akt) pathway and reduced tumor invasion.[30,31] In SKH-1 hairless mice, luteolin delayed the development of UVB-induced tumors, reduced tumor multiplicity and the overall size of tumors. Furthermore, luteolin inhibited the COX-2, AP-1, NF-κB and Akt signaling pathway both in SHK-1 hairless mouse skin and in the mouse epidermal cell line JB6 P+. This effect was achieved by direct suppression of the upstream kinases PKCε, a calcium-independent protein kinase and c-Src, a nonreceptor tyrosine kinase. PKCε is involved in UV-induced skin damage, hyperplasia, elevated TNF-α levels and the development of squamous cell carcinoma.[32] c-Src is otherwise closely related to proliferation, metastasis, angiogenesis[33] and its activation is an initial step in the UV-induced signaling cascade.[27,34] Therefore, luteolin might be beneficial in preventing skin cancer development. Interestingly, luteolin increased only the survival of healthy keratinocytes whereas the sensitivity of malignant keratinocytes from squamous cell carcinomas was unchanged.[35] It was also shown that luteolin exerts pro-oxidative effects on the human melanoma cell line A2058 by inducing apoptisis through ER stress via increasing ROS levels. This effect might exert selective cytotoxicity to cancer cells with no effect on normal cells.[36] Furthermore, luteolin reduced dose-dependently UVB-induced skin inflammation in healthy volunteers as effective as 1% hydrocortisone.[37] In the highly invasive epidermoid carcinoma cell line A431 luteolin could also inhibit metastases by reversing epithelial-mesenchymal transition (EMT). In this process, luteolin induced the expression of the epithelial biomarker E-cadherin and repressed the expression of the mesenchymal markers N-cadherin and vimentin.[38,39] Luteolin might inhibit metastasis of these cancer cells by blocking the Akt/mTOR/c-Myc signaling pathway that suppress the ribosomal protein S-19 (RPS19)-activated EMT process.[40] Furthermore, the epidermal growth factor (EGF) was overexpressed in A431 cells resulting in MMP-9 overexpression and induction of EMT. Luteolin also reduced the expression of EGF and MMP-9.[38,39]

Concerning photoaging, luteolin reduced the UV-induced release of pro-inflammatory cytokines from keratinocytes and fibroblasts, for example, IL-6, TNF-α and IL-20. IL-20 might play a special role in photoaging, because the wrinkled skin of *IL-20* transgenic mice looks like the dermal abnormalities of photoaged skin.[14] The IL-20 heterodimeric receptor complex consists of the subunit IL20R1 and IL20R2 and is expressed on human dermal fibroblasts.[41] The effect of luteolin might be attributed to its anti-oxidative and radical scavenging activities, leading to reduced amounts of ROS (e.g., hydrogen peroxide) in the skin or to a reduced release of IL-20 and other pro-inflammatory cytokines from ROS-activated keratinocytes.[42,43] As a consequence, the MMP-1 production was reduced in fibroblasts, so that collagen fragmentation as key driver of photoaging could be prevented.[43] Besides, collagen and hyaluronic acid (HA) as the major non-fibrous components in dermis and epidermis play an essential role in protecting the skin from dryness by its capacity to bind water.[44] The content of HA in the epidermis and dermis decreased after UVB irradiation due to ROS-mediated decreased synthesis and increased degradation of HA.[45] Importantly, luteolin inhibited hyaluronidase activation and thus prevented the degradation of HA. A direct link between UVB-induced collagen cleavage and the loss of HA synthesis might exist via collagen fragment-induced inhibition of Rho kinases during skin aging.[46] Another way to reduce photoaging is the use of hyaluronidase and collagenase inhibitors that block already active enzymes. Luteolin is also a potent hyaluronidase inhibitor.[43] Furthermore, luteolin could also directly inhibit UVA-induced MMP-1 production in the keratinocyte cell line HaCaT by inhibiting the Ca^{2+}influx and in this way the phosphorylation of Ca^{2+}/calmodulin-dependent MAPKs. This led finally to a reduced binding of AP-1 (heterodimer of c-Jun and c-Fos) to its promotor and a reduced MMP1 expression.[47]

Taken together, luteolin may protect human keratinocytes and fibroblasts from the deleterious effects of UV radiation by complex UV-absorbing,

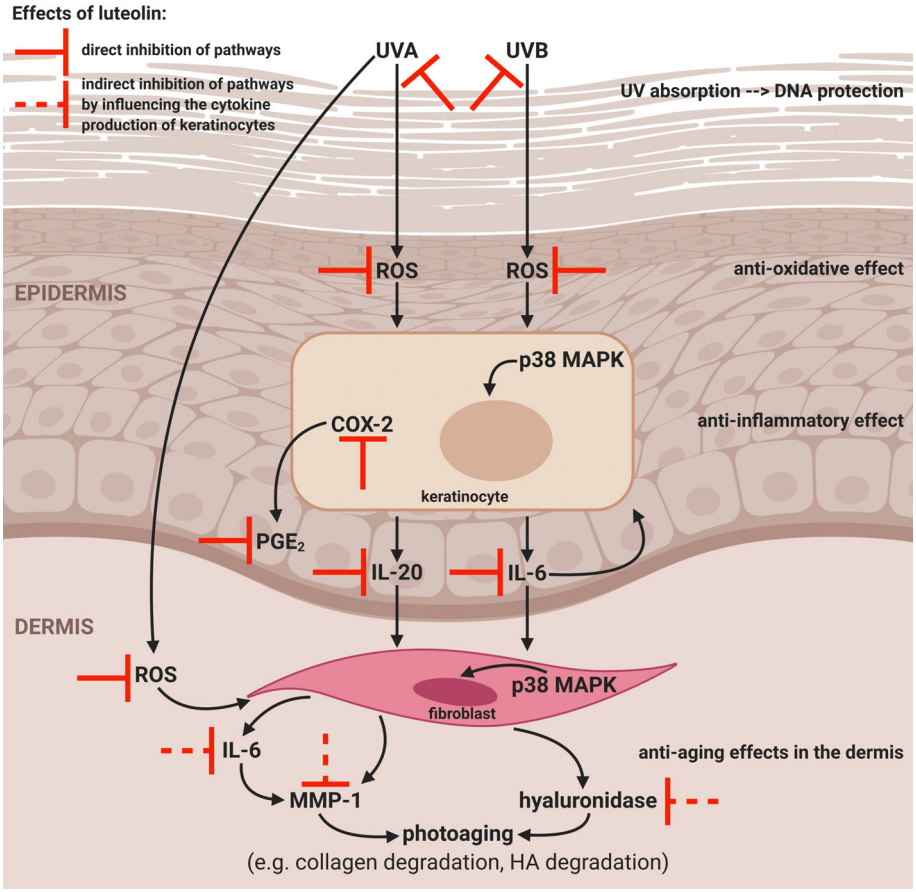

FIGURE 2 Beneficial effects of luteolin on photoaging, skin aging and skin cancer. UVA and UVB radiation can partially be absorbed by luteolin, thereby decreasing their adverse effects in the skin by acting as a first line of defense. UV-induced ROS production in the skin is also counteracted by luteolin through stabilization of radical species and the inhibition of pro-oxidant enzymes and induction of anti-oxidant enzymes. UV-induced pro-inflammatory signaling pathways have been shown to be efficiently inhibited by luteolin, typical targets being COX-2 or NF-κB-dependent cytokines like IL-6. In the last step, the anti-aging effects of luteolin in the dermis are achieved by inhibiting different enzymes like hyaluronidase and MMPs

DNA-protective, anti-oxidative and anti-inflammatory properties (Figure 2). This is important because even a low dose UVB exposure is sufficient to cause DNA damage in human skin cells,[48] so that luteolin might be beneficial in preventing skin cancer development. Furthermore, it indicates that luteolin is a promising candidate for the prevention/reduction of photoaging effects.

3 | WOUND HEALING

The skin as one of the largest organ of the human body constitutes the first barrier against invading pathogens. Disruption of its structural integrity results in the formation of wounds. The wound healing process consists of four phases: hemostasis, inflammation, proliferation and remodeling. Each of these phases contains a variety of steps that enable an efficient and successful closure of a wound. The immediate reaction to a skin injury is trying to stop bleeding from vascular injuries. In addition to contraction of the vessels, clot formation and the activation of platelets are essential for an efficient hemostasis. It was shown that luteolin treatment reduced in vitro clot mass and fibrin polymer formation as well as inhibited the pro-coagulant enzymes thrombin and factor X and platelets.[49,50] Interestingly, these effects were similar to those observed with aspirin, but they are reversible and seem to counteract wound healing at this early stage. In the inflammatory phase of wound healing, similar effects of luteolin as described in psoriasis can be expected, as many cells affecting psoriasis are also present in wounds. Prolonged inflammation can be detrimental to wound healing, because it may cause new tissue damage and delays the proliferation of skin cells. Therefore, reduced leukocyte migration and plasma leakage after luteolin treatment[51] might be beneficial after the initial immune response in wounds. In the proliferative phase, angiogenesis is one of the key steps to achieve an efficient wound healing response. However, luteolin is known for its prominent anti-angiogenic abilities. These are characterized by an inhibition of vascular endothelial growth factor (VEGF) signaling leading to an inhibition of survival and proliferation of endothelial cells.[52] Although this is counterproductive for wound healing it might be beneficial for the treatment of diseases like gastric cancer.[53,54] The first skin cells that start to close the wound are fibroblasts. They are stimulated to proliferate and migrate by factors released from hemostatic clots. This process can be assisted by luteolin, because it increases fibroblast proliferation in different in vitro assays.[55] Then the proliferating fibroblasts start to produce molecules (e.g., different types of collagen and fibronectin) to set the first layer of

extracellular matrix (ECM). Again, luteolin mainly seems to counteract wound healing, because of its ability to reduce the production of collagen I, collagen III and fibronectin as well as the proliferation of the producing fibroblasts.[56] However, luteolin is able to inhibit the activity of hyaluronidase and collagenase, leading to a more stable ECM.[57] On this newly formed ECM, keratinocytes migrate from the edges of the wound until they form a complete sheet of cells. LUT-7G showed an increased wound healing ability of keratinocytes by the expression of the proliferation marker Ki67 and proteins like cyclin D1 that regulate the cell cycle. Furthermore, proliferation assays like the BrdU assay together with a scratch assay demonstrated that keratinocytes exhibit an increased wound healing ability after LUT-7G treatment.[58] After wound closure, myofibroblasts start to contract the wound area to reduce the area needing to heal. Luteolin treatment prevents contractility of these cells and the ECM by inhibiting the TGF-β signaling[59] and thereby counteracts wound retraction. In the final stage of wound healing, the ECM has to be remodeled by a combination of synthesis, degradation and reorganization of matrix molecules to form an intact epithelium. In this phase, the LUT-7G-mediated inhibition of collagenases might inhibit the reorganization of the ECM and appear again contradictory.[57]

Taken together, many results point toward a detrimental effect of luteolin and its structural analogs on wound healing. However, most of these studies were performed with in vitro test systems typically using only one cell type so that the complexity of the actual skin in the wound healing process is not considered. LUT-7G, for example, shows in either incision or excision wounds of a murine wound model a significantly increased rate of wound closure and tensile length, with values of 39.9% and 31.2%, respectively.[57] Similar results were achieved in a wound model using diabetic and non-diabetic rats. Luteolin treatment resulted in faster wound healing with a higher tensile strength, more collagen, a better epithelial regeneration and less inflammation.[60]

In conclusion, although many in vitro results contradict the use of luteolin for wound healing especially in the early phases, in vivo wound healing studies point to a beneficial effect.

4 | INFLAMMATORY SKIN DISEASES

4.1 | Psoriasis

Psoriasis is a chronic inflammatory disease manifested in the skin and the joints of patients. With a global prevalence of 2%–3%, psoriasis influences over 125 million people. The most common form of psoriasis, psoriasis vulgaris, accounts for about 90 % of all cases and is characterized by sharply demarcated erythematous and indurated plaques covered by silvery lamellar scales. Luteolin with its anti-inflammatory and anti-oxidant properties might be beneficial for psoriasis patients with less side effects in comparison to synthetic active components. The immune reaction in psoriasis can be triggered by unspecific insults like trauma or chemical irritants leading to the release of DNA and RNA from keratinocytes. These nucleotides form complexes with antimicrobial peptides (AMPs) in the skin and activate innate immune cells like neutrophils or dendritic cells (DCs) via their Toll-like receptors (TLRs). In response to this TLR activation, neutrophils start to release ROS and neutrophil extracellular traps (NETs). NETs contain, for example, RNA molecules that can bind AMPs and create a feedback loop for further (self-) activation of neutrophils and other innate immune cells.[61] Luteolin can inhibit the signaling of different TLRs on cells like plasmacytoid DCs, mast cells or neutrophils (Figure 3). This inhibition is achieved by reducing TLR and TLR target gene expression,[62] blocking the formation of TLR signaling complexes or inhibition of downstream signaling molecules like TBK1 and components of the MAPK/ERK pathway.[63–66] The release of NETs and ROS by neutrophils could also be reduced by luteolin.[64] In a more cell specific context, Ye and colleagues could show that luteolin treatment in mice reduced the number of CD11c + DCs with the costimulatory signals necessary for T-cell activation and survival, that is, CD80 or CD86.[67] Furthermore, luteolin reduced the IL-12 and TNF-α release by DCs.[68] As shown, mast cells are major producers of IL-22 and to a lesser extent of IL-17. These are both important cytokines of psoriasis. In addition, other pro-inflammatory cytokines like TNF-α or IL-6 are also released by mast cells and contribute to the pro-inflammatory milieu in the skin of psoriasis. Both luteolin and its structural analog 3′,4′,5,7-tetramethoxyluteolin inhibited these actions of mast cells.[56,69] Once the innate immune system is fully activated, these cells release cytokines and drive the activation and differentiation of naïve T cells into T_H1, T_H17 and T_H22 cells. Verbeek and colleagues could show that luteolin had a profound effect on T cell proliferation and the secretion of IFN-γ[70] and might therefore contribute to a reduction of psoriasis. In addition, the release of IL-17A by T cells, a key step during the development of psoriasis and target of the monoclonal antibody Secukinumab, could also be inhibited by luteolin.[67] Furthermore, luteolin influences the differentiation of T cells. In a murine psoriasis model,

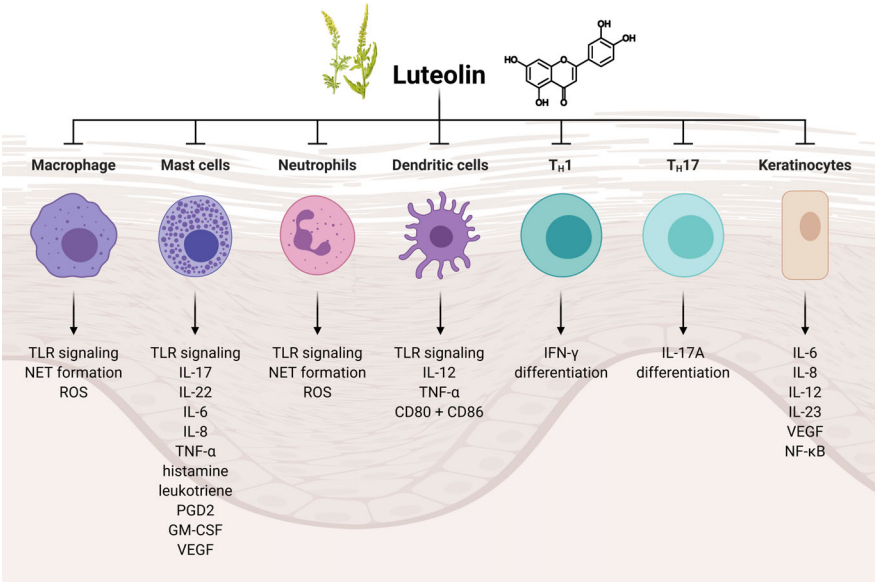

FIGURE 3 Potential therapeutical targets for luteolin in psoriasis and dermatitis. In a variety of in vitro and in vivo studies luteolin has shown promising abilities in inhibiting or interfering with a variety of pro-inflammatory signaling pathways in different (immune) cell types. This is achieved by either directly interacting with signaling molecules or by changing conditions like the redox status that lead to the activation of pathways

treatment with luteolin could reduce the percentage of T_H1 and T_H17 cells while T_H2 and Treg cells were increased.[71]

In response to the cytokines released by T cells and innate immune cells, keratinocytes on the one hand are activated and trigger pro-inflammatory signaling pathways and on the other hand start to proliferate. This proliferation exceeds the normal levels of cell division and leads to the hyperproliferative, undifferentiated phenotype typical for psoriatic skin. Luteolin was able to reduce the production and release of pro-inflammatory cytokines like IL-6 and IL-8 in an in vitro setting using HaCaT cells and normal human epidermal keratinocytes by inhibiting NF-κB signaling.[72] Similar anti-inflammatory effects concerning the release of IL-6, IL-8 and VEGF from HaCaT keratinocytes were achieved by an inhibition of the mTOR pathway using 3′,4′,5,7-tetramethoxyluteolin.[73] Concerning the lack of differentiation and the hyperproliferation of psoriatic keratinocytes, Palombo and colleagues were able to reduce the block of keratinocyte differentiation with luteolin-7-glucoside (LUT-7G) in vitro as shown by keratin 1 and 10 expression.[74] In addition to their cell culture studies, they used a murine in vivo psoriasis model and could confirm the results of LUT-7G concerning the reduction of epidermal proliferation and scale thickness as well as the increase of the differentiation markers loricrin and keratin 10. This model also showed the anti-inflammatory capabilities of LUT-7G by inhibiting the IL-22-induced nuclear translocation of pSTAT3. Similar in vivo results were found in murine studies with luteolin-7-O-β-D-glucuronide.[75] A very recent study confirmed these results with luteolin and could also show an effect of luteolin leading to suppression of nitric oxide, iNOS and COX-2.[76] In addition, LUT-7G inhibited the cellular energy production of keratinocytes by an interaction with hexokinase 2 that leads to a depression of the glycolytic and Krebs pathway.[74] However, studies on the effect of luteolin in psoriasis patients are still scarce. Only four psoriasis patient were treated with a skin lotion twice a day containing 3′,4′,5,7-tetramethoxyluteolin and showed after 1 month of application a beneficial effect of their psoriasis symptoms.[77]

Extensive work is still needed to confirm the promising results of the in vitro and in vivo psoriasis mouse studies as well as the small patient study.

4.2 | Contact dermatitis and atopic dermatitis

Contact dermatitis is an acute or chronic sterile inflammatory skin disease resulting in erythema and eczema formation. It occurs due to (repeated) skin contact with environmental xenobiotic chemicals. According to the definition of the European Society for Contact Dermatitis (ESCD), there are four different forms of contact dermatitis: irritative contact dermatitis (ICD) and allergic contact dermatitis (ACD), photocontact dermatitis (being triggered after either photoirritant or -allergen in the skin is exposed to UV-light) and contact urticaria as type 1 allergic reaction, mediated by a specific IgE response to high molecular weight protein allergens. ICD is mediated by the direct activation of cellular- and tissue- stress and -damage reactions leading to the activation of innate immune cells and inflammatory responses. In contrast,

ACD as a classical delayed-type (IV) T-cell mediated allergy additionally requires the binding of low molecular weight organic chemicals or metal ions to proteins and subsequently not only the activation of the innate immune system but also the activation of an adaptive immune response.[78]

Although an estimated 15%–20% of the population suffer from ACD and the deciphering of the ACD pathogenesis has increasingly focused on the mechanisms that trigger innate immune responses in recent years, there is still a lack of valid therapeutic options. Unfortunately, the gold standard is still the avoidance of the causative allergen and treatment with corticosteroids with their known side effects. One interesting (adjuvant) therapeutic approach could be a dietary change with appropriate intake of food or beverages containing substances with anti-allergic activity such as luteolin, thus possibly allowing at least a reduction of corticosteroid treatment. Another approach might be the topical use of such substances for the reduction of inflammation in irritative and/or allergic contact dermatitis.

Such an approach has been chosen by Schempp et al.[79] to address the effectiveness of *Reseda luteola* (L.) derived luteolin in a human irritation model. In a standardized repeated washing test with the irritant sodium lauryl sulfate, a cream containing the antioxidant luteolin significantly reduced the redness and transepidermal water loss of the irritated skin and improved the hydration of the *stratum corneum* in 25 healthy volunteers. The same extract also reduced UVB mediated skin inflammation in vivo as mentioned above.[37] This indicates that the anti-oxidative effect of luteolin can protect from skin irritation induced by frequent washing and water-soluble irritants (such as e.g., diluted acids and alkalis, alcohol, detergents and disinfectants) as well as UV mediated skin irritation.

Apart from *Reseda luteola*, other plants containing luteolin have been analyzed for their potential to reduce skin inflammation, as well. Among those is *Bryophyllum pinnatum* (Lam.) Oken (Crassulaceae), which has been shown to contain the flavonoids rutin, quercetin, luteolin and luteolin7-O-β-d-glucoside. While in this case the direct effect of luteolin alone was not analyzed, the ethanol leaf extract was able to reduce both acute and chronic murine ear edema induced by several different irritants (croton oil, arachidonic acid, phenol, capsaicin and ethyl phenylpropiolate).[80] This supports the concept that flavonoids such as luteolin can suppress innate immune responses underlying extremely inflammatory conditions such as irritative dermatitis.

Recently, mast cells have been shown to act as key promotors of ACD, mediating the adjuvant effect of haptens.[81] Interestingly, luteolin inhibits immunoglobulin E mediated histamine, leukotriene, prostaglandin D_2 (PGD_2) and granulocyte macrophage-colony stimulating factor (GM-CSF) release of mast cells derived from human umbilical cord blood in a concentration dependent manner[82] (Figure 3). This effect was even stronger with the novel structural luteolin analog 3′,4′,5,7-tetramethoxyluteolin (methoxyluteolin) in direct comparison to luteolin.[83] Furthermore, it was shown that methoxyluteolin is able to inhibit neuropeptide (substance P or neurotensin) mediated TNF-α, IL-8 and VEGF release by inhibiting mTOR activation in mast cells.[84] mTOR activation has also been shown to be essential in IFN-γ activated keratinocytes by inducing the expression of IL-12 and IL-23. As a result naïve T cells differentiate to Th1 and Th17 cells[85] that are both involved in ACD.[78] In addition, Kempuraj et al. have shown that luteolin pre-treatment prevents mast cell activation, Jurkat T cell activation and mast cell mediated Jurkat activation after stimulation of cells with myelin basic protein.[86] Therefore, it is tempting to suggest that luteolin reduces inflammation by inhibiting mast cell activation and thereby prevents ACD. Indeed, topical application of pure (98%) luteolin dissolved in olive oil inhibited the scratching behavior in an egg albumin induced murine passive cutaneous anaphylaxis model and reduced the inflammatory reaction both in an irritative and an ACD model.[87] The authors speculated that inhibition of mast cell activation was involved in the pruritus reduction. However, they also concluded that further factors could be involved, because luteolin also inhibited the scratching behavior in mice treated with compound 48/80, which induces scratching independent of mast cell mediators.[87]

Further effects of luteolin on ACD were observed by Góngora et al., who analyzed the effect of an *Phagnalon rupestre* (L.) DC. (Asteraceae) methanol extract on 2,4-dinitrofluorbenzene induced ACD and a sheep red blood cell induced hypersensitivity reaction.[88] Eight active compounds including luteolin 7-O-beta-glucoside were identified in the extract. All were tested for dinitrofluorobenzene-induced contact hypersensitivity inhibitory activity. Luteolin 7-O-beta-glucoside was the most active with an ACD inhibition rate of 49% and 79% inhibition at 24 and 96 h, respectively.[88] The authors speculated that -due to the early observed inhibitory effect after application of a single dose of the extract- the inhibition might be mediated by an interference with the initial phases of elicitation such as lymphocyte dependent mast cell activation, neutrophil degranulation but potentially also by an inhibition of protein kinase C and/or inhibition of ICAM-1 expression. Luteolin is known to inhibit protein kinase C,[89] an enzyme involved in the efficient migration of Langerhans cells, and effectively

inhibit ICAM-1 expression and MAPK activation,[90] which also play an important role not only in psoriasis but also in ACD development.

Moreover, we and others have shown that the production of ROS by contact sensitizers is essential for the induction of the sensitization phase of ACD and that inhibition of ROS generation by anti-oxidants such as luteolin was able to abrogate both the sensitization- as well as the elicitation phase in the murine model for ACD, the contact hypersensitivity (CHS) model.[13] In addition, luteolin prevented the release of pro-inflammatory cytokines by keratinocytes and fibroblasts and suppressed the activation of hyaluronidases, thereby preventing the breakdown of (anti-inflammatory) high molecular weight HA into (pro-inflammatory, TLR2 and TLR4 agonistic) low molecular weight HA fragments.[13] Upstream of cytokine expression, luteolin inhibited NF-kB activation by targeting IKK activation in murine bone marrow derived dendritic cells and in a NF-kB reporter mouse in vivo,[68] also known to be essential for the induction of ACD. Another effect of luteolin potentially involved in the down modulation of ACD might be an enhanced expression of anti-inflammatory cytokines like IL-10 as well as an enhanced induction of FOXP3-expressing CD4+ CD25+ regulatory T cells as observed, for example, after intraperitoneal application of luteolin in an OVA-induced asthma model.[91] In addition, the effect of cynaroside (CYR, also known as luteoloside), the 7-O-glucoside of luteolin, on ACD was recently analyzed by Szekalska et al.[92] CYR was extracted from the aerial parts of *Bidens tripartita* L. (Asteraceae), and applied in a purity of 95% in a hydrogel formulation containing alginate (ALG), an anionic polymer with bioadhesive properties. The hydrogel formulation with CYR was able to inhibit inflammation in a carrageenan-induced mouse paw edema model as well as to reduce ear swelling responses in an oxazolone mediated CHS model. This is in line with the effects of CYR observed by Palombo et al. regarding the inhibition of psoriatic inflammation[74] and further underlines the multifaceted effects of luteolin in the inhibition of inflammatory skin reactions.

Regarding other forms of dermatitis, Jo et al. have analyzed the effects of an ethanol extract of the aerial parts of *Stellera chamaejasme* L. (Thymelaeaceae) on oxazolone- or 2,4-dinitrochlorobenzene stimulated murine models of atopic dermatitis (AD).[93] *Stellera chamaejasme* contains diverse flavonoids and coumarins with anti-oxidative, anti-viral and anti-cancer activities as well as anti-inflammatory, analgesic and wound healing activities and exerted anti-atopic properties in the AD models. In addition, the major active compound of the EtOH extract, luteolin 7-O-glucoside, decreased serum IgE and IL-4 levels, epidermal thickening as well as transepidermal water loss and increased skin hydration, therefore, showing strong anti-atopic dermatitis activity.[93] In addition, in the proliferative canine keratinocyte cell line CPEK, luteolin down modulated expression of IL-33, IL-1β, IL-6 and IL-8 after lipopolysaccharide (LPS) stimulation, indicating that luteolin might also enable the treatment of canine atopic dermatitis.[94]

Interestingly, luteolin as the active component of *Perilla frutescens* L. (Lamiaceae) was also shown to inhibit the production of IL-4 in a house dust mite (HDM) induced murine Balb/c model of allergic rhinitis. This was also seen in mononuclear cells from peripheral blood of allergic rhinitis patients restimulated with HDM.[95] This indicates that not only type IV hypersensitivity reactions or AD but also type 1 reactions can be suppressed by luteolin and that due to the effect of luteolin on IgE and IL-4 luteolin might also reduce contact urticaria reactions (Figure 3).

5 | CONCLUSION

Luteolin possesses a significant potential to inhibit or even reverse signs of skin diseases such as psoriasis, dermatitis, wound healing and UV-induced diseases such as skin cancer and photoaging. Therefore, luteolin is a promising molecule warranting the development of topic formulations and systemic agents. The natural character and the high effectiveness are favorable features and might replace known preparations with limited usefulness.

ACKNOWLEDGMENTS

Figures 2 and 3 were created with BioRender.com. Open access funding enabled and organized by Projekt DEAL.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated.

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How to cite this article: Gendrisch F, Esser PR, Schempp CM, Wölfle U. Luteolin as a modulator of skin aging and inflammation. *BioFactors*. 2021;47: 170–180. https://doi.org/10.1002/biof.1699