



# Molecular targets of quercetin with anti-inflammatory properties in atopic dermatitis

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Atopic dermatitis (AD) is an inflammatory skin disease. Over the past few decades, AD has become more prevalent worldwide. Quercetin, a naturally occurring polyphenol, shows antioxidant, anti-inflammatory, and antiallergic activities. Several recent clinical and preclinical findings suggest quercetin as a promising natural treatment for inflammatory skin diseases. Significant progress in elucidating the molecular mechanisms underlying the anti-AD properties of quercetin has been achieved in the recent years. Here, we discuss the use of quercetin as treatment for AD, with a particular focus on the molecular basis of its effect. We also briefly discuss the approaches to improve the bioavailability of quercetin.

## Introduction

AD is the most ubiquitous pediatric inflammatory skin disorder, which has a variety of causes, including environmental, psychological, immunological, pharmacological, and genetic factors [1]. AD currently affects millions of children and adults worldwide and this is expected to increase two-threefold over the next few decades. Approximately 50% of those with AD develop symptoms during childhood, with 95% of such patients being less than 5 years of age when the symptoms first manifest. Around 50–75% of children with early-onset AD are sensitized to allergens, such as food allergens, house dust mites, or pets, whereas those with late-onset AD are often less sensitized. Children with severe AD have a 50% risk of developing bronchial asthma and a 75% risk of developing hay fever [2].

An exact understanding of the mechanism underlying AD is lacking, which makes it difficult to develop more-efficient management strategies. AD skin lesions are characterized by increased infiltration of inflammatory cells, such as monocytes, eosinophils,

macrophage, mast cells, and activated T helper cells (Th1 and Th2) [3]. Therefore, drugs that inhibit all of these cells could be expected to exhibit prompt therapeutic effects. Immune-suppressive topical or systemic steroids and/or calcineurin inhibitor therapies quickly result in AD improvement and have been in use for decades; however, their long-term usage can result in an extensive range of adverse effects. Moreover, the long-term use of steroids leads to local reactions, such as skin atrophy, telangiectasia, hypertrichosis, and topical steroid addiction [4]. Recently, plant polyphenols, such as quercetin, resveratrol, naringenin, and tannic acid, have emerged as therapeutic alternatives for the treatment of AD [5–7]. Flavonoid or polyphenol quercetin is found in most vegetables and edible fruits, particularly in apples, nuts, herbs, onions, and cherry wines. This flavonoid has various biological activities, which are mainly related to its ability to inhibit enzymes and its effects on immune responses [8]. The pharmacological effects of quercetin, such as its antioxidant, anti-inflammatory, antiallergic, antiaging, and anticancer activities, as well as its regulating effect on interleukin (IL)-6, IL-8, tumor necrosis factor (TNF) $\alpha$ , histamine, and tryptase release in mast cells, are well acknowledged [9]. However, there has been less focus on the effects of quercetin on

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skin inflammation and AD, despite its use in experimental animal models and human clinical studies in recent years. Thus, here we review the current evidence that supports the use of quercetin as an anti-inflammatory and antiallergic agent. We also discuss the possible mechanisms by which quercetin ameliorates skin inflammation and AD. In addition, we highlight the problem of quercetin bioavailability and ways in which it could be improved.

### Molecular mechanisms underlying AD

The hallmarks of AD are a chronic, worsening form of skin inflammation, the disturbance of skin barrier function, which results in dry skin, and immunoglobulin E (IgE)-mediated sensitization to allergens [10]. The histological features of AD skin include hyperkeratosis, acanthosis with varying degrees of spongiosis, parakeratosis, and exocytosis of mononuclear cells in the epidermis and a prominent perivascular infiltrate of lymphocytes, dendritic cells (DCs), and a few eosinophils in the dermis [7]. Moreover, T lymphocytes have an essential role in the pathogenesis of AD, with marked infiltration of activated cluster of differentiation (CD)4+ and CD8+ T cells in the skin. AD is characterized by an imbalance between Th1 and Th2 resulting from the presence of a specific IgE response in association with Th2 immune responses [11]. In AD, Th2 cells produce a variety of cytokines, including IL-4, IL-5, IL-9 and IL-13, which are important in stimulating Th1 immune responses [12]. The most extensive studies indicate that AD has a complex pathogenesis, with the activation of multiple inflammatory and immunological signaling pathways [13]. An understanding of the relative roles of these factors in AD pathogenesis has been made possible by manipulating various proteins and pathways, such as (i) high-mobility group protein 1 (HMGB1) signaling; (ii) activation of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway; and (iii) activation of thymic stromal lymphopoietin (TSLP) protein (Fig. 1).

#### The HMGB1 signaling pathway

Nonhistone nuclear protein HMGB1 is a proinflammatory cytokine associated with the development of several clinical conditions, including AD, psoriasis, arthritis, sepsis, and autoimmune diseases [14]. It is mainly secreted from immune cells, such as DCs, monocytes, macrophages, and damaged and/or necrotic cells. Extracellular HMGB1 can interact with receptor for advanced glycation end products (RAGE), Toll-like receptor 2 (TLR2) and TLR4; there is also a possibility that different regions in HMGB1 interact with different receptors [6]. Several studies have demonstrated that RAGE, TLR2, and TLR4 interactions with HMGB1 activate the nuclear factor kappa B (NF- $\kappa$ B) pathway to mediate the cytokine activity that is involved in inflammation and oxidative stress in AD [7]. In addition, the interaction of RAGE with HMGB1 activates the extracellular signal-regulated kinase (ERK)1/2 and NF- $\kappa$ B signaling pathway. Recent reports suggest that ERK1/2 and NF- $\kappa$ B signaling are involved in inflammatory skin disease and that inhibitors of this pathway ameliorated inflammation in various rodent models of human skin diseases [15]. A similar scenario has been described for NF- $\kappa$ B, and activation of RAGE can induce downstream signaling, such as NF- $\kappa$ B expression in inflamed AD skin in mice. NF- $\kappa$ B transcription factors also stimulate the transcription of Th1 and Th2 cytokines, currently a focus of research interest.

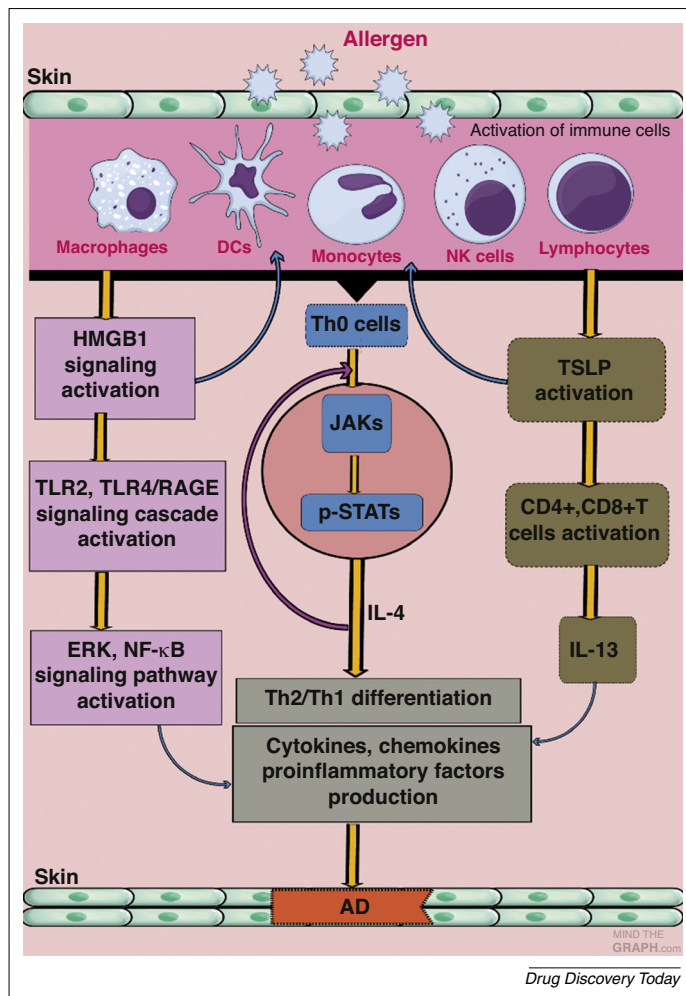


FIGURE 1

Schematic diagram for the possible modulation of immune cell-mediated inflammatory responses in atopic dermatitis (AD). Allergens are taken up by immune cells and activate downstream danger signaling molecules, such as thymic stromal lymphopoietin (TSLP), high-mobility group protein 1 (HMGB1), and the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, which then leads to the alteration of balance between T helper 1 (Th1) and Th2 cells. These cells encourage the production of cytokines, chemokines, and proinflammatory factors that leads to AD-like skin lesions. Please see the main text for further definitions of the abbreviations in this figure.

The above findings clearly suggest that activated HMGB1 interacts with TLR2, TLR4, and RAGE to activate downstream signaling that leads to inflammation in animal models of AD. Numerous reports have demonstrated that quercetin inhibits HMGB1 translocation and its downstream cascade signaling pathway in the skin of AD mice [16]. Similarly, in another study, quercetin treatment prevented lipopolysaccharide (LPS)-induced HMGB1 release and proinflammatory functions [17]. Moreover, quercetin has been reported to have an inhibitory role in other signaling pathways, namely the tyrosine-phosphorylated phosphatidylinositol-3-kinase (PI3K) and myeloid differentiation factor 88 association signaling pathway and the mitogen-activated protein kinase (MAPK)/activator protein 1 (AP1) and I $\kappa$ B kinase (IKK)/NF- $\kappa$ B pathway, which induce the production of inflammatory mediators in macrophages [18].

### JAK-STAT signaling

JAK-STAT signaling is a classic signal transduction pathway for several cytokines and growth factors. The ligands binding to their receptors leads to JAK activation, which in turn phosphorylates and causes STAT activation. The activated STATs translocate to the cell nucleus, where they regulate gene expression [19]. In that AD is a Th2-dominant disease, IL-4 signaling activates the JAK-STAT6 pathway to regulate Th2-related target genes in AD lymphocytes [20]. Studies have shown that activated mast cells enhance the production of Th2 cytokines and attenuate the secretion of Th1 cytokines; mast cells or histamine activated JAK-STAT signaling, which triggered IL-13 production in a murine Th2 cell line [21]. Another study suggested that activated histamine suppresses STAT1 activation through H4 receptors on T cells, which drives the Th2 response, leading to the development of AD.

In many cases, the cytokine receptors recruit JAK family members [JAK1, JAK2, JAK3, and tyrosine kinase 2 (Tyk2)] into signaling complexes; thus, genetic deletion of JAK2 mice resulted in embryonic lethality due to defects in erythropoiesis [22]. Consequently, local suppression of JAK1/JAK2 could be therapeutic in inflammatory skin diseases by limiting systemic JAK inhibition. STAT3 has important part in inflammatory skin diseases, as well as in normal keratinocyte function. Increased phosphorylated STAT3 levels were observed in AD skin lesions and keratinocyte-controlled expression of a constitutively active STAT3 in mice resulted in skin lesions with striking similarity to those in humans with AD [20]. Thus, JAK-STAT signaling represents a promising therapeutic target for the treatment of AD.

Quercetin has been shown to inhibit the JAK-STAT pathway in inflammatory diseases. Moreover, *in vitro* treatment of activated T cells with quercetin blocked IL-12-induced tyrosine phosphorylation of JAK2, TYK2, STAT3, and STAT4, resulting in decrease T cell proliferation and Th1 differentiation [23]. Thus, the anti-inflammatory nature of quercetin has a role in the attenuation of AD by modulating the TLR2 and JAK2/STAT3 pathways and inhibiting STAT3 tyrosine phosphorylation within inflamed cells [24]. The cytokine-mediated upregulation of inducible nitric oxide synthase (iNOS) and intercellular adhesion molecule 1 (ICAM-1) via the JAK-STAT cascade was abolished by quercetin treatment [25]. Hamalainen *et al.* [26] reported that quercetin inhibited LPS-induced STAT1 activation along with its inhibitory effect on iNOS and NF- $\kappa$ B expression, which are involved in the activation of several inflammatory genes.

### Activation of TSLP

Levels of TSLP, an epithelial-derived cytokine with a role in Th2 immunity, are significantly increased in human AD skin as well as blood. Recent animal studies suggest that keratinocyte-produced TSLP is involved as a link between AD and asthma [27]. TSLP signaling is initiated via a heterodimer comprising the IL-7 receptor  $\alpha$  chain and TSLP receptor (TSLPR), which was originally characterized by its ability to promote the activation of B lymphocytes and myeloid DCs [28]. TSLP is also expressed by primary skin keratinocytes, smooth muscle cells, and lung fibroblasts. It can perform its biological functions through its action on many different types of cell [29]. TSLP can activate CD4+ T cells and CD8+ T cells in mice and differentiates B cells in humans, which enhances the release of T cell-attracting chemokines from

monocytes. In addition, TSLP can enhance the secretion of Th2 cytokines in human mast cells. The binding of activated TSLP with its receptor complex can activate multiple signal transduction pathways [30]. A recent study reported that the activation of the TSLP-IL-7R/TSLPR complex induced phosphorylation of the JAK-STAT signaling pathway, leading to skin inflammation [31].

Furthermore, DCs in damaged skin develop an activated phenotype, leave the epidermis, and migrate towards the draining lymph node, consistent with a role for TSLP in the regulation of tissue-resident DC responses [32]. Higher expression of TSLP in the skin epidermis drives the development of spontaneous skin inflammatory disease, with hallmarks of human AD. Another study reported that TSLP signaling was required for the development of AD [33]. TSLPR-deletion mice failed to express Th2 cytokines induced locally by CD4+ T cells as they infiltrate the skin, which appeared to be responsible for inflammatory skin disease development [34]. Thus, targeting the TSLP signaling axis via pharmacological inhibition could be an appropriate approach for AD treatment. It was demonstrated that quercetin and tannic acid effectively suppressed vascular endothelial growth factor (VEGF), thymus and activation-regulated chemokine (TARC), and TSLP expression in human keratinocytes, and also suppressed proinflammatory cytokine and CD31 expression in AD skin lesions [35].

### Molecular targets of quercetin

Numerous extensive studies have demonstrated that oxidative or inflammatory factors, such as proinflammatory factors, cytokines, and chemokines, have an essential role in the pathogenesis of AD; therefore, recently, plant polyphenols have emerged as a therapeutic alternative for the treatment of AD with a low risk of adverse effects. Quercetin and its derivatives are major flavonoids in the human diet and have been demonstrated to have several beneficial effects, including antioxidant, anti-inflammatory, antitumor, and antiallergic actions. Recently, *in vitro* and *in vivo* experimental studies demonstrated that quercetin is a potent pleiotropic molecule and that interacts with several molecular targets (Box 1). Quercetin and its derivatives have been demonstrated to activate or increase the expression of various antioxidant enzymes and genes, such as nuclear factor (erythroid-derived 2)-like (Nrf2), peroxisome proliferator-activated receptor (PPAR) $\alpha$ , PPAR $\gamma$ , and heme oxygenase 1 (HO-1). By contrast, they are effective downregulators of HMGB1, NF- $\kappa$ B, STAT1, TSLP, protein kinases, chemokines, cytokines, and proinflammatory biomarkers [16,24]. Below, we discuss the antioxidant, anti-inflammatory, and antiallergic activities of quercetin and its derivatives in preventing and ameliorating the complications of skin diseases, with a focus on AD.

### Antioxidant effects of quercetin on skin inflammation

Based on its polyphenol structure, quercetin has potent antioxidant effects, whereby it combines with free radical species to make markedly less-reactive phenoxy radicals [36]. Moreover, quercetin reduces oxidative stress-induced cell death in keratinocytes through its antioxidant actions [37]. Another study reported that quercetin-3-O-(2'-galloyl)- $\alpha$ -L-rhamnopyranoside prevented oxidative stress-induced apoptosis in human keratinocytes by suppressing the caspase 8 and mitochondrial pathway [38]. Numerous studies indicate the involvement of reactive oxygen species (ROS)

## BOX 1

## Molecular targets of quercetin and its derivatives

Structural names of quercetin and its derivatives		Gene expression
3,5,7,3',4'-Pentahydroxyflavon (quercetin)	RAGE	Heat shock protein 75 kDa
Quercetin 3-O-glucoside (isoquercetin)	TLR2, 4	Poly (ADP-ribose) polymerase 1
Quercetin 3-O-rhamnoside (quercitrin)	TNF receptor 1, 2	Tumor protein p53
Quercetin 3-O-rhamnosyl-(1-6)-glucoside-rutin	TNF receptor-associated factor 6	Voltage dependent anion-selective channel protein 1
Quercetin 5-methyl ether (azaleatin)	Liver X receptor $\alpha$ , $\beta$	
Quercetin 7-methyl ether (rhamnetin)	Epidermal growth factor receptor	
Quercetin 3'-methyl ether (isorhamnetin)	C-C chemokine receptor type 1, 5	
Quercetin 4'-methyl ether (tamarixetin)	Histamine H1 receptor	
Quercetin 7-methoxy-3-O-glucoside		
Quercetin 3'-methoxy-3-O-galactoside		
Transcriptional factors	Enzymes	Others
AP1	Transforming growth factor $\beta$ -activated kinase 1	Histamine
HMGB1	PI3K	58k-9 Golgi protein
NF- $\kappa$ B (p65, p50)	PKC	Prostaglandin E2, D2
Nrf2	HO-1	VEGF
NF- $\kappa$ B inhibitor $\alpha$	NOS	IgE
Proliferator-activated receptor $\gamma$	IL-1 receptor-associated kinase 1	Granulocyte-macrophage colony-stimulating factor
PPAR $\alpha$	ERK1/2	Ferric-reducing ability of plasma
Inflammatory cytokines	Tryptase	Intracellular calcium level
IL-1 $\beta$ , 4, 5, 8, 10, 13, 33	$\beta$ Hexosaminidase	Superoxide anion, peroxynitrite
Interferon $\gamma$	Histidine decarboxylase	Glutathione
Chemokines (CCL2, 3, 11, 17, 27)	Ribosomal protein s6 kinase $\beta$ 1	B cell lymphoma extra-large 2
TNF- $\alpha$	Serum paraoxonase/arylesterase 2	Cytochrome C
TSLP	P38 MAPK	ATP-binding cassette subfamily A, member 1
Leukotriene B4	c-Jun N-terminal kinases	
Macrophage inflammatory protein 1 $\alpha$	JAK	
Fc epsilon RII	Spleen tyrosine kinase	
STAT1	Proto-oncogene tyrosine protein kinase	
	Cathepsin K	
	PKA	
	Matrix metalloproteinase 9	
	Caspase 3	
	NADH oxidase	

in different physiological functions and several cell signaling processes during inflammation. ROS stimulated by NADPH oxidase have emerged as important messengers of several cellular signaling pathways, including the activation of the NF- $\kappa$ B and AP-1 signaling pathway in skin inflammation [39]. It has been demonstrated that inhibition of NF- $\kappa$ B can attenuate oxidative stress and improve skin inflammation.

The transcriptional activator Nrf2 is ubiquitously indicated in many organs as phase II genes joining antioxidant responsive element (ARE) sequences [40]. Nrf2 acts when released from its repressive cytosolic protein Keap1. Upon exposure of cells to oxidative stress, electrophilic compounds, or covalently transformed thiol groups, Nrf2 is quickly translocated from cytoplasmic Keap1 to the nucleus, where it binds to transactivate antioxidant enzyme genes [16]. Increasing evidence has shown that activation of Nrf2 signaling attenuates oxidative stress in inflammatory skin diseases by facilitating phase II antioxidant enzymes, such as HO-1. In contrast, Nrf2-deficient mice exhibit greater induction of proinflammatory genes regulated by NF- $\kappa$ B, such as *IL1b*, *TNF $\alpha$* , and cyclooxygenase 2 (*COX2*), suggesting that Nrf2 deficiency enhances NF- $\kappa$ B-mediated proinflammatory reactions [41]. Moreover, experimental studies have also investigated the Nrf2-ARE pathway interplay via the inhibitory regulation of

HMGB1 secretion from macrophages and/or monocytes. Quercetin was shown to defend effectively against oxidative stress and to attenuate inflammation in house dust mite-induced AD mice by activating Nrf2 signaling [16]. In addition, similar studies reported that treatment with quercetin activated Nrf2 levels and prevented the activation of the MAPK and NF- $\kappa$ B pathway in human keratinocytes [42].

### Anti-inflammatory properties of quercetin on skin inflammation

Quercetin and its derivatives exert potent anti-inflammatory effects. Recent studies have shown that quercetin suppressed proinflammatory cytokine expression through modulation of NF- $\kappa$ B and p38 MAPK in a human mast cell line [43]. In addition, treatment with a novel quercetin derivative, quercetin-3-O-(2''-gallate)- $\alpha$ -L-rhamnopyranoside, suppressed inflammatory cytokines, such as IL-4, 5 and 13, serum IgE, eosinophil levels, iNOS, and COX2 in the AD NC/Nga mouse model [44]. Some of the most important targets of quercetin are the proinflammatory cytokines, HMGB1, RAGE, and ERK1/2-NF- $\kappa$ B downstream signaling proteins, which have a major role in mediating inflammatory responses by modulating the production of proinflammatory cytokines in AD NC/Nga mouse skin [16].

Treatment with quercetin adequately suppressed the levels of inflammatory and proinflammatory cytokines through PPAR $\alpha$  upregulation and also improved skin barrier dysfunction in AD [45]. Recent data suggested that activated macrophages participate in skin barrier dysfunction and inflammatory responses by releasing proinflammatory cytokines, such as TNF $\alpha$  and inflammatory factors in AD skin lesions. Interestingly, quercetin attenuates the NF- $\kappa$ B/cAMP response element binding protein (CRE)/AP-1 signaling pathway in murine macrophages [39]. In addition, it was demonstrated that quercetin inhibited proinflammatory cytokines, such as IL-1 $\beta$ , IL-6, and TNF $\alpha$ , and increased IL-10 levels in LPS-induced inflammation in mice [46]. Furthermore, the activation of IL-6 pleiotropic cytokines triggered Th2 or mast cell activation in AD skin lesions. Interestingly, quercetin was more effective compared with the mast cell stabilizer cromolyn in blocking human mast cell cytokine release and inhibited dermatitis and photosensitivity in humans [9].

### Antiallergic effect of quercetin on skin inflammation

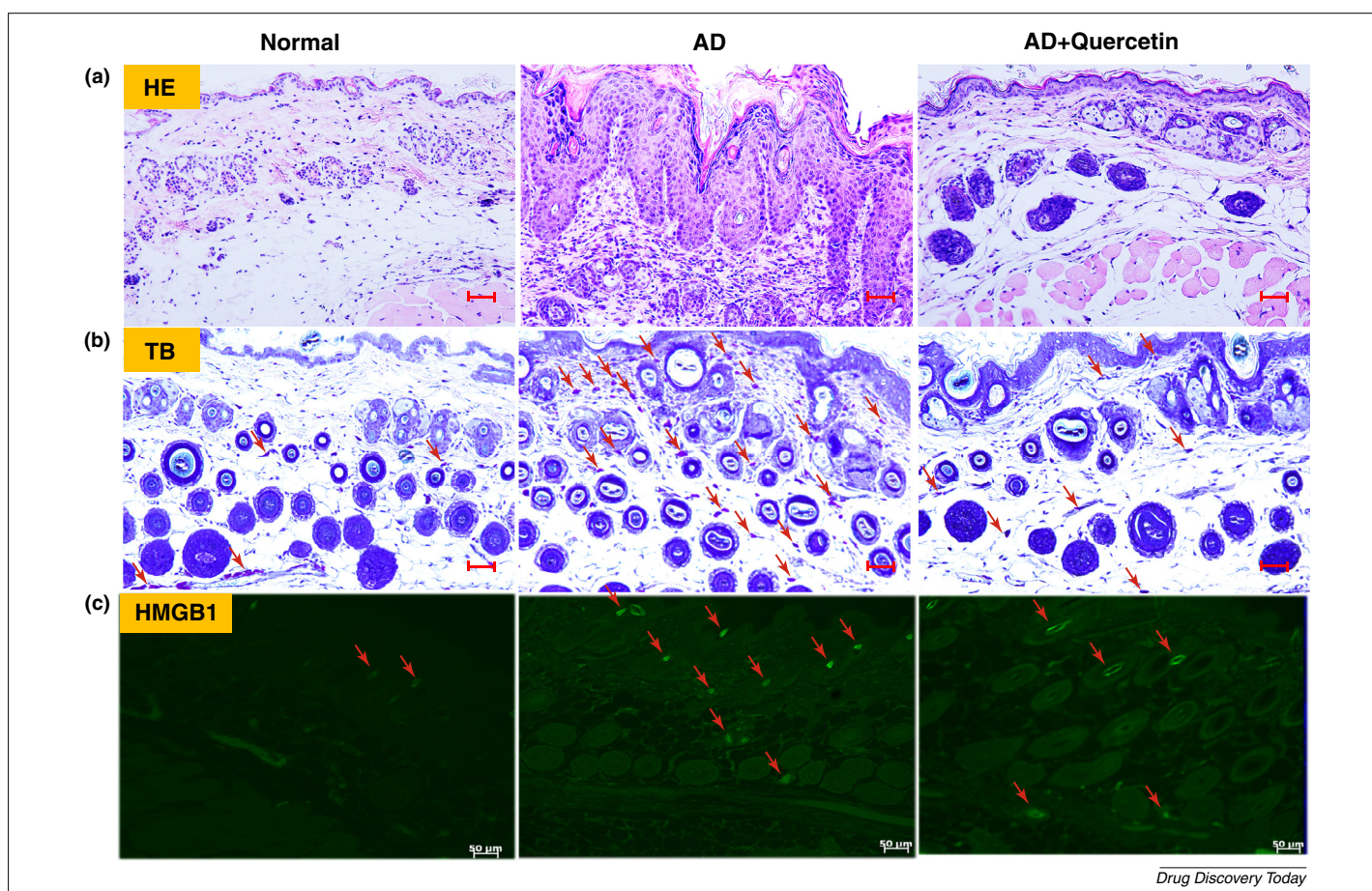
Quercetin has been shown to ameliorate symptoms linked with AD, including allergic skin diseases. The anti-inflammatory effect of quercetin treatment significantly suppressed inflammatory

cytokines, such as IL-4 and IL-5, as well as NF- $\kappa$ B expression in an allergic inflammatory mouse model [47]. Moreover, quercetin can inhibit human neutrophil elastase-induced MUC5AC expression in human epithelial cells through the protein kinase C (PKC)/ERK signal transduction pathway [48]. A recent study reported quercetin to exert antiallergic actions via activation of the Nrf2–HO-1 signaling pathway in rodent mast cells [49]. Furthermore, a novel powerful quercetin derivative, quercetagenin, regulated the STAT1 signaling pathway during the production of TARC and macrophage derived chemokine (MDC) by IFN $\gamma$  and TNF $\alpha$  stimulation in HaCaT human keratinocytes [50].

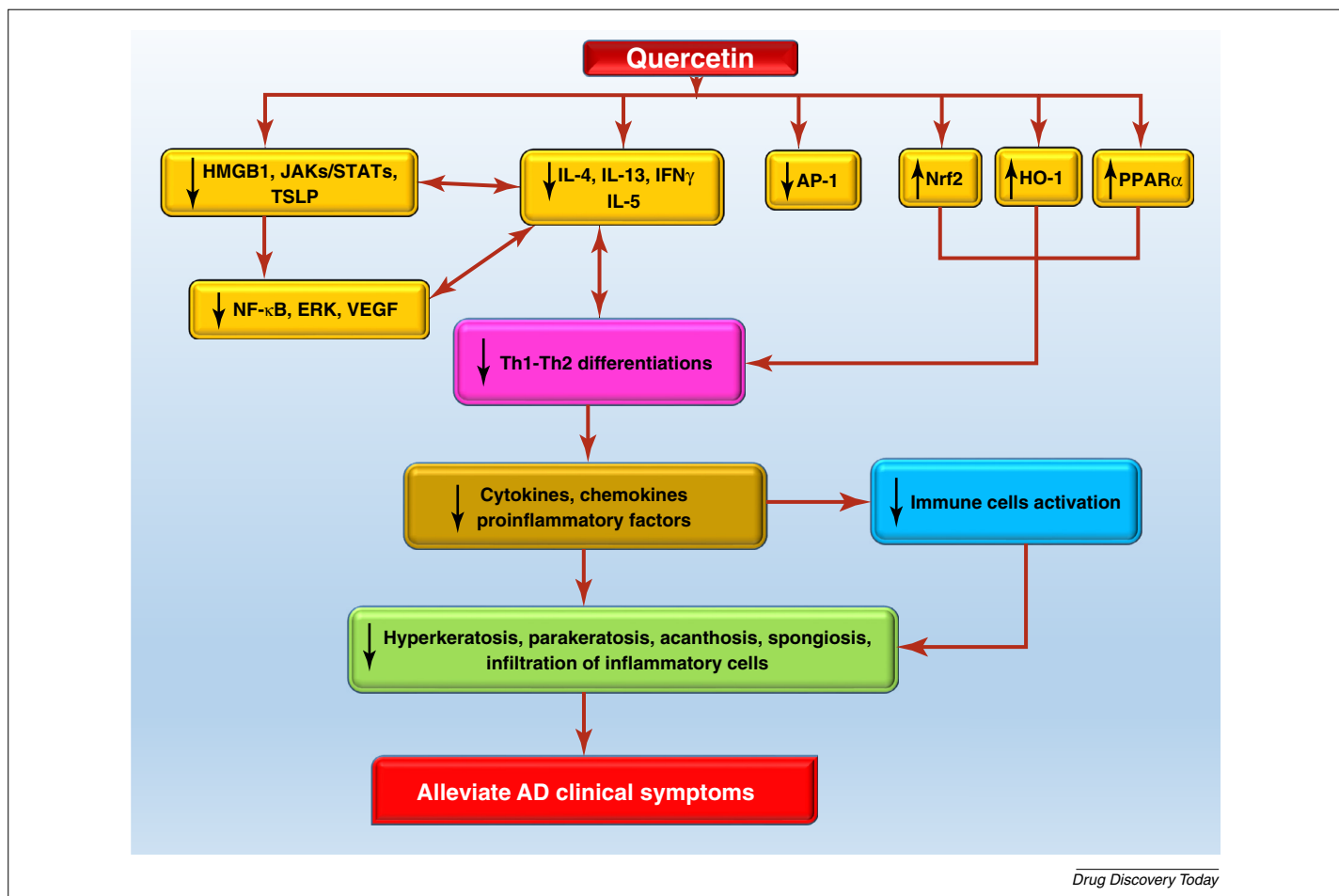
Taken together, the above data suggest that quercetin suppresses inflammation, oxidative stress, allergic inflammation, and inflamed skin, thereby ameliorating the pathological changes that occur in AD (Figs 2 and 3). However, its potency is broadly limited by its poor bioavailability. Thus, the effectual formulation of quercetin has been designed with the aim of improving its pharmacokinetics and physiochemical properties.

### Quercetin pharmacokinetics

Although polyphenols are important constituents in the human diet, they show poor aqueous solubility and instability. These



**FIGURE 2** Ameliorative effects of quercetin in skin inflammation. **(a)** Hematoxylin–eosin (HE) staining of cross-sectional tissue slices of skin showing hyperkeratosis, parakeratosis, acanthosis, spongiosis, and infiltration of inflammatory cells. **(b)** Skin levels of mast cells (red arrow) determined by toluidine blue (TB) staining. **(c)** Immunofluorescence determination of high-mobility group protein 1 (HMGB1)-positive cells (red arrow). Key: normal, age-matched normal NC/Nga mice; AD, atopic dermatitis (AD)-induced NC/Nga mice; AD + Quercetin, AD-induced mice treated with quercetin (50 mg/kg/day orally).

**FIGURE 3**

Molecular targets modulated by quercetin. Down arrow (black) indicates downregulated molecular targets; up arrow (black) indicates upregulated molecular targets. Please see the main text for definitions of the abbreviations in this figure.

properties of quercetin result in its poor bioavailability, permeability, and extensive first-pass metabolism before entering the systemic circulation. Administration of a quercetin-containing diet (50 or 500 mg/kg) to rats for 11 weeks resulted in the wide circulation of quercetin metabolites in body tissues. A quercetin diet (500 mg/kg) administered to pigs for 3 days revealed the presence of quercetin in tissues, including the liver (3.8 nmol/g) and kidneys (1.8 nmol/g). Other tissues, such as brain, heart, and spleen, contained only a low concentration (~0.12 nmol/g) of quercetin. Similarly, only 20% of radiolabeled quercetin orally administered to rats was absorbed [51]. A similar scenario was described in another study, in which plasma samples did not contain any detectable levels of aglycone in weanling rats administered quercetin in the diet at 0.45% for a period of 6 weeks [52]. Another similar study reported that quercetin (8, 20 and 50 mg) administered orally to 16 humans was detected in plasma as the glucuronide- and sulfate-conjugated and unconjugated forms with a dose-dependent increase in  $C_{max}$  (0.14, 0.22, and 0.29  $\mu\text{M}$ , respectively) [53]. Pharmacokinetic studies of quercetin have demonstrated that its poor absorption and rapid metabolism are the major causes of its poor bioavailability. Drug delivery systems, such as emulsions, liposomes and phospholipid formulations, nanocrystals, inclusion complexes, polymer nanoparticles, and

micelles, are used to improve quercetin solubility and bioavailability [54]. The administration of quercetin-loaded nanovesicles achieved an important reduction in local vascular permeability, epidermal loss, and leukocyte infiltration, and increased bioavailability and stability [55,56]. A similar study reported that the topical application of quercetin-loaded lipid-based nanovesicles improved its solubility and vesicular bilayer fluidity, and also transiently reduced the stratum corneum barrier function [57]. A recent study revealed that the combination of microneedles with lipid microparticles increased the topical delivery of quercetin in pig skin [58]. In addition, a nanostructured lipid carrier formulation enhanced the dermal delivery of quercetin [59]. Thus, further understanding of the pharmacokinetic profile of quercetin could improve its internal and topical bioavailability.

### Clinical trials with quercetin and its derivatives

In a recent trial, 52 patients with moderate to severe AD received orally administered quercetin and its derivatives (kaempferol, rutin) containing whey associated with dodder seed in a water extract formulation at a dose of 2 g per day for 15 days; this resulted in the attenuation of AD severity and decreased inflammation, which suggests that quercetin and its derivatives could be used to treat patients with moderate to severe AD [60]. A quercetin

capsule administered orally at the same dose was demonstrated to decrease nickel patch-induced contact dermatitis and also to suppress ultraviolet (UV)B-induced skin erythema in patients [9]. Moreover, in patients with sarcoidosis, quercetin reduced markers of inflammation, such as TNF $\alpha$  and IL-8 [61]. Another study reported that quercetin did not alter blood leukocytes subsets, macrophage activity, IL-6, or TNF $\alpha$  plasma levels in healthy females [62]. In addition a supplement of 1200 mg glucosamine hydrochloride, 60 mg chondroitin sulfate and 45 mg quercetin (GCQ) per day effectively decreased clinical symptoms in patients with knee osteoarthritis [63]. Thus, quercetin, with its multiple intracellular targets and lack of toxicity, could be particularly useful in formulations that increase its solubility and bioavailability for the treatment of AD and other inflammatory skin diseases [9].

### Concluding remarks

The mechanistic studies that we have illustrated briefly here suggest the possible beneficial effects of quercetin in inflammatory skin diseases, such as AD. Extensive *in vitro* and *in vivo* research in

animal models has shown multiple mechanisms of action that could suppress inflammatory cytokines and proinflammatory factors in patients with AD. Quercetin, which is considered to be nontoxic and pharmacologically safe for human use, and its derivatives are versatile molecules that should be investigated more extensively for their broader application in human AD, including their therapeutic actions. However, we are still lacking definitive evidence for the precise mechanism of action by which quercetin might ameliorate AD in humans. Thus, future research should focus on determining this mechanism as well as on improving the bioavailability of quercetin. In addition, more controlled, randomized human clinic trials are required to confirm the efficacy and optimal dosage of quercetin, to further confirm its promise for the treatment of AD and other inflammatory skin diseases.

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### References

- Udompataikul, M. and Limpa-o-vart, D. (2012) Comparative trial of 5% dexpantenol in water-in-oil formulation with 1% hydrocortisone ointment in the treatment of childhood atopic dermatitis: a pilot study. *J. Drugs Dermatol.* 11, 366–374
- Thomsen, S.F. (2014) Atopic dermatitis: natural history, diagnosis, and treatment. *ISRN Allergy* 2014, 354250
- Won, T.J. *et al.* (2011) Oral administration of *Lactobacillus* strains from Kimchi inhibits atopic dermatitis in NC/Nga mice. *J. Appl. Microbiol.* 110, 1195–1202
- Lee, J.K. *et al.* (2010) Inhibitory effects of heartwood extracts of *Broussonetia kazinoki* Sieb on the development of atopic dermatitis in NC/Nga mice. *Biosci. Biotechnol. Biochem.* 74, 1802–1806
- Kim, M.J. and Choung, S.Y. (2012) Mixture of polyphenols and anthocyanins from *Vaccinium uliginosum* L. alleviates DNCB-induced atopic dermatitis in NC/Nga mice. *Evid. Based Complement. Alternat. Med.* 2012, 461989
- Karuppagounder, V. *et al.* (2014) Resveratrol attenuates HMGB1 signaling and inflammation in house dust mite-induced atopic dermatitis in mice. *Int. Immunopharmacol.* 23, 617–623
- Karuppagounder, V. *et al.* (2015) Tannic acid modulates NF $\kappa$ B signaling pathway and skin inflammation in NC/Nga mice through PPAR $\gamma$  expression. *Cytokine* 76, 206–213
- Hollman, P.C. *et al.* (1995) Absorption of dietary quercetin glycosides and quercetin in healthy ileostomy volunteers. *Am. J. Clin. Nutr.* 62, 1276–1282
- Weng, Z. *et al.* (2012) Quercetin is more effective than cromolyn in blocking human mast cell cytokine release and inhibits contact dermatitis and photosensitivity in humans. *PLoS ONE* 7, e33805
- Novak, N. *et al.* (2003) Immune mechanisms leading to atopic dermatitis. *J. Allergy Clin. Immunol.* 112 (6 Suppl.), S128–S139
- Choi, J.K. and Kim, S.H. (2013) Rutin suppresses atopic dermatitis and allergic contact dermatitis. *Exp. Biol. Med. (Maywood)* 238, 410–417
- Leung, D.Y. *et al.* (2003) New concepts in the pathogenesis of atopic dermatitis. *Curr. Opin. Immunol.* 15, 634–638
- McClean, W.H. and Irvine, A.D. (2013) Old King coal: molecular mechanisms underlying an ancient treatment for atopic eczema. *J. Clin. Invest.* 123, 551–553
- Chen, T. *et al.* (2013) Increased HMGB1 serum levels and altered HMGB1 expression in patients with psoriasis vulgaris. *Arch. Dermatol. Res.* 305, 263–267
- Ipaktschi, K. *et al.* (2006) Topical p38MAPK inhibition reduces dermal inflammation and epithelial apoptosis in burn wounds. *Shock* 26, 201–209
- Karuppagounder, V. *et al.* (2015) Modulation of HMGB1 translocation and RAGE/NF $\kappa$ B cascade by quercetin treatment mitigates atopic dermatitis in NC/Nga transgenic mice. *Exp. Dermatol.* 24, 418–423
- Tang, D. *et al.* (2009) Quercetin prevents LPS-induced high-mobility group box 1 release and proinflammatory function. *Am. J. Respir. Cell Mol. Biol.* 41, 651–660
- Endale, M. *et al.* (2013) Quercetin disrupts tyrosine-phosphorylated phosphatidylinositol 3-kinase and myeloid differentiation factor-88 association, and inhibits MAPK/AP-1 and IKK/NF- $\kappa$ B-induced inflammatory mediators production in RAW 264.7 cells. *Immunobiology* 218, 1452–1467
- Bao, L. *et al.* (2013) The involvement of the JAK-STAT signaling pathway in chronic inflammatory skin disease atopic dermatitis. *JAKSTAT* 2, e24137
- Boos, A.C. *et al.* (2014) Atopic dermatitis, STAT3- and DOCK8-hyper-IgE syndromes differ in IgE-based sensitization pattern. *Allergy* 69, 943–953
- Horr, B. *et al.* (2006) STAT1 phosphorylation and cleavage is regulated by the histamine (H4) receptor in human atopic and non-atopic lymphocytes. *Int. Immunopharmacol.* 6, 1577–1585
- Neubauer, H. *et al.* (1998) Jak2 deficiency defines an essential developmental checkpoint in definitive hematopoiesis. *Cell* 93, 397–409
- Muthian, G. and Bright, J.J. (2004) Quercetin, a flavonoid phytoestrogen, ameliorates experimental allergic encephalomyelitis by blocking IL-12 signaling through JAK-STAT pathway in T lymphocyte. *J. Clin. Immunol.* 24, 542–552
- Liao, Y.R. and Lin, J.Y. (2014) Quercetin, but not its metabolite quercetin-3-glucuronide, exerts prophylactic immunostimulatory activity and therapeutic antiinflammatory effects on lipopolysaccharide-treated mouse peritoneal macrophages *ex vivo*. *J. Agric. Food Chem.* 62, 2872–2880
- Senggunprai, L. *et al.* (2014) Quercetin and EGCG exhibit chemopreventive effects in cholangiocarcinoma cells via suppression of JAK/STAT signaling pathway. *Phytother. Res.* 28, 841–848
- Hamalainen, M. *et al.* (2007) Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF- $\kappa$ B activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF- $\kappa$ B activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. *Mediators Inflamm.* 2007, 45673
- Zhu, Z. *et al.* (2011) The role of TSLP in IL-13-induced atopic march. *Sci. Rep.* 1, 23
- Briot, A. *et al.* (2009) Kallikrein 5 induces atopic dermatitis-like lesions through PAR2-mediated thymic stromal lymphopoietin expression in Netherton syndrome. *J. Exp. Med.* 206, 1135–1147
- Wilson, S.R. *et al.* (2013) The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. *Cell* 155, 285–295
- Zhong, J. *et al.* (2014) TSLP signaling pathway map: a platform for analysis of TSLP-mediated signaling. *Database (Oxford)* 2014, bau007
- Arima, K. *et al.* (2010) Distinct signal codes generate dendritic cell functional plasticity. *Sci. Signal.* 3, ra4
- Bogiatzi, S.I. *et al.* (2007) Cutting Edge: proinflammatory and Th2 cytokines synergize to induce thymic stromal lymphopoietin production by human skin keratinocytes. *J. Immunol.* 178, 3373–3377
- Yoo, J. *et al.* (2005) Spontaneous atopic dermatitis in mice expressing an inducible thymic stromal lymphopoietin transgene specifically in the skin. *J. Exp. Med.* 202, 541–549
- Larson, R.P. *et al.* (2010) Dibutyl phthalate-induced thymic stromal lymphopoietin is required for Th2 contact hypersensitivity responses. *J. Immunol.* 184, 2974–2984

- 35 Jung, M.K. *et al.* (2010) Tannic acid and quercetin display a therapeutic effect in atopic dermatitis via suppression of angiogenesis and TARC expression in Nc/Nga mice. *J. Invest. Dermatol.* 130, 1459–1463
- 36 Yang, H.H. *et al.* (2014) Quercetin-3-O-beta-D-glucuronide isolated from *Polygonum aviculare* inhibits cellular senescence in human primary cells. *Arch. Pharm. Res.* 37, 1219–1233
- 37 Potenza, L. *et al.* (2008) Effect of quercetin on oxidative nuclear and mitochondrial DNA damage. *Biofactors* 33, 33–48
- 38 Kim, Y.J. *et al.* (2013) Quercetin-3-O-(2'-galloyl)-alpha-L-rhamnopyranoside prevents TRAIL-induced apoptosis in human keratinocytes by suppressing the caspase-8- and Bid-pathways and the mitochondrial pathway. *Chem. Biol. Interact.* 204, 144–152
- 39 Kim, B.H. *et al.* (2013) Relative antioxidant activities of quercetin and its structurally related substances and their effects on NF-kappaB/CRE/AP-1 signaling in murine macrophages. *Mol. Cells* 35, 410–420
- 40 Kang, C.H. *et al.* (2013) Quercetin inhibits lipopolysaccharide-induced nitric oxide production in BV2 microglial cells by suppressing the NF-kappaB pathway and activating the Nrf2-dependent HO-1 pathway. *Int. Immunopharmacol.* 17, 808–813
- 41 Li, W. *et al.* (2008) Activation of Nrf2-antioxidant signaling attenuates NFkappaB-inflammatory response and elicits apoptosis. *Biochem. Pharmacol.* 76, 1485–1489
- 42 Ding, M. *et al.* (2010) Inhibition of AP-1 and MAPK signaling and activation of Nrf2/ARE pathway by quercitrin. *Int. J. Oncol.* 36, 59–67
- 43 Min, Y.D. *et al.* (2007) Quercetin inhibits expression of inflammatory cytokines through attenuation of NF-kappaB and p38 MAPK in HMC-1 human mast cell line. *Inflamm. Res.* 56, 210–215
- 44 Park, E.J. *et al.* (2015) Effect of topical application of quercetin-3-O-(2''-gallate)-alpha-L-rhamnopyranoside on atopic dermatitis in NC/Nga mice. *J. Dermatol. Sci.* 77, 166–172
- 45 Kim, B. *et al.* (2014) *Eruca sativa* and its flavonoid components, quercetin and isorhamnetin, improve skin barrier function by activation of peroxisome proliferator-activated receptor (PPAR)-alpha and suppression of inflammatory cytokines. *Phytother. Res.* 28, 1359–1366
- 46 Liao, Y.R. and Lin, J.Y. (2015) Quercetin intraperitoneal administration ameliorates lipopolysaccharide-induced systemic inflammation in mice. *Life Sci.* 137, 89–97
- 47 Rogero, A.P. *et al.* (2010) Anti-inflammatory effect of quercetin-loaded microemulsion in the airways allergic inflammatory model in mice. *Pharmacol. Res.* 61, 288–297
- 48 Li, N. *et al.* (2012) The effect of quercetin on human neutrophil elastase-induced mucin5AC expression in human airway epithelial cells. *Int. Immunopharmacol.* 14, 195–201
- 49 Matsushima, M. *et al.* (2009) Heme oxygenase-1 mediates the anti-allergic actions of quercetin in rodent mast cells. *Inflamm. Res.* 58, 705–715
- 50 Kang, G.J. *et al.* (2013) Anti-inflammatory effect of quercetagenin, an active component of immature *Citrus unshiu*, in HaCaT human keratinocytes. *Biomol. Ther. (Seoul)* 21, 138–145
- 51 Chen, X. *et al.* (2005) Pharmacokinetics and modeling of quercetin and metabolites. *Pharm. Res.* 22, 892–901
- 52 Graf, B.A. *et al.* (2006) Rat gastrointestinal tissues metabolize quercetin. *J. Nutr.* 136, 39–44
- 53 de Boer, V.C. *et al.* (2005) Tissue distribution of quercetin in rats and pigs. *J. Nutr.* 135, 1718–1725
- 54 Cai, X. *et al.* (2013) Bioavailability of quercetin: problems and promises. *Curr. Med. Chem.* 20, 2572–2582
- 55 Castangia, I. *et al.* (2014) Fabrication of quercetin and curcumin bionanovesicles for the prevention and rapid regeneration of full-thickness skin defects on mice. *Acta Biomater.* 10, 1292–1300
- 56 Manca, M.L. *et al.* (2014) Improvement of quercetin protective effect against oxidative stress skin damages by incorporation in nanovesicles. *Colloids. Surf. B: Biointerfaces* 123, 566–574
- 57 Caddeo, C. *et al.* (2014) Topical anti-inflammatory potential of quercetin in lipid-based nanosystems: *in vivo* and *in vitro* evaluation. *Pharm. Res.* 31, 959–968
- 58 Paleco, R. *et al.* (2014) Enhancement of the *in vitro* penetration of quercetin through pig skin by combined microneedles and lipid microparticles. *Int. J. Pharm.* 472, 206–213
- 59 Chen-yu, G. *et al.* (2012) Development of a quercetin-loaded nanostructured lipid carrier formulation for topical delivery. *Int. J. Pharm.* 430, 292–298
- 60 Mehrbani, M. *et al.* (2015) The efficacy of whey associated with dodder seed extract on moderate-to-severe atopic dermatitis in adults: a randomized, double-blind, placebo-controlled clinical trial. *J. Ethnopharmacol.* 172, 325–332
- 61 Pfeuffer, M. *et al.* (2013) Effect of quercetin on traits of the metabolic syndrome, endothelial function and inflammation in men with different APOE isoforms. *Nutr. Metab. Cardiovasc. Dis.* 23, 403–409
- 62 Furst, R. and Zundorf, I. (2014) Plant-derived anti-inflammatory compounds: hopes and disappointments regarding the translation of preclinical knowledge into clinical progress. *Mediators Inflamm.* 2014, 146832
- 63 Kanzaki, N. *et al.* (2012) Effect of a dietary supplement containing glucosamine hydrochloride, chondroitin sulfate and quercetin glycosides on symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled study. *J. Sci. Food Agric.* 92, 862–869