# Proanthocyanidins: A novel approach to Henoch-Schonlein purpura through balancing immunity and arresting oxidative stress via TLR4/MyD88/NF-κB signaling pathway (Review)

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**Abstract.** Henoch-Schonlein purpura (HSP), a recurrent and immunoglobulin (Ig)A-mediated vasculitis, presents not only as skin lesions but also as systemic involvement that can be life-threatening. Although the etiology of HSP remains unknown, immune imbalance and oxidative stress (OS) are primary contributors to its pathogenesis, alongside the abnormal activation of Toll-like receptor (TLR)/myeloid differentiation primary response gene 88 (MyD88)/nuclear factor-κB (NF-κB) pathway. TLRs, especially TLR4, stimulate downstream signaling molecules such as NF-κB and proinflammatory cytokines, which are released when TLRs combine with the key adapter molecule MyD88. This leads to the activation of T helper (Th) cell 2/Th17 and overproduction of reactive oxygen species (ROS). The function of regulatory T (Treg) cells is suppressed in the process. Th17/Treg imbalance then produces various inflammatory cytokines to promote proliferation and differentiation of B cells and the secretion of antibodies. IgA is secreted, and it binds to vascular endothelial surface receptors where the complex induces injury of the vascular endothelial cells. Additionally, excessive ROS creates OS that leads to an inflammatory response and vascular cell apoptosis or necrosis, thereby contributing to vascular endothelial damage and HSP occurrence. Proanthocyanidins are active compounds naturally enriched in fruits, vegetables and plants. Proanthocyanidins have diverse properties, including anti-inflammatory, antioxidant, antibacterial, immunoregulatory, anticarcinogenic and vascular protective effects. Proanthocyanidins are used in the management of various diseases. Proanthocyanidins regulate T cells, equilibrate immunity and arrest OS by inhibiting the TLR4/MyD88/NF-κB signaling pathway. Considering the pathogenesis of HSP and the properties of proanthocyanidins, the present study hypothesized that these compounds may potentially lead to HSP recovery through modulating the immune equilibrium and preventing OS by inhibiting the TLR4/MyD88/NF-κB pathway. To the best of our knowledge, however, little is known about the positive effects of proanthocyanidins against HSP. The present review summarizes the potential of proanthocyanidins to treat HSP.

**Contents**



## 1. Introduction

Henoch-Schonlein purpura (HSP) is an immunoglobulin (Ig)A-mediated relapsing vasculitis that invades small arteries and capillaries of the skin and other organs, such as gastrointestinal tract and kidneys. It primarily manifests as cutaneous purpura, joint swelling, digestive symptoms (mainly abdominal pain) and kidney injury, which can be fatal (1,2). Based on clinical features, HSP is classified into five categories: Simple, arthritis, abdominal, renal and mixed types (3). HSP frequently occurs in children, affecting 3-27 children per 100,000 population; but there has been an increasing

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number of incidents in adults who possibly suffer more serious systemic issues due to age (4). To the best of our knowledge, the pathogenesis of HSP has not been completely elucidated; however, immune imbalance and oxidative stress (OS) that induce IgA-mediated vascular damage may be involved (5,6). It is also hypothesized that toll-like receptor (TLR)4/myeloid differentiation primary response gene 88 (MyD88)/nuclear factor-κB (NF-κB) signaling is involved (7). Various treatments have been applied to HSP, including anti-inflammatory drugs, anti-histamine, vitamin C, calcium, corticosteroids, cytotoxic drugs and immunosuppressants, as well as blood-activating and stasis-resolving medicines (8-10). However, these therapies exhibit poor efficacy and do not stop recurrence, research has shown that relapses occur in about 25% of patients and that children over age 8 or those with kidney-based disease are more prone to relapse (11); furthermore, most approaches to HSP are unsuitable for long-term application owing to high expenditures and adverse side effects, e.g. long-term and large-scale use of glucocorticoids could cause infections and Cushing's syndrome; long-term use of cytotoxic drugs that could result in gastrointestinal reactions, hepatotoxicity, bone marrow suppression, reproductive toxicity, cardiotoxicity (12). Thus, a novel and effective cure for HSP is required.

Proanthocyanidins are a class of natural polyphenolic compounds that consist of epicatechin and catechin. Proanthocyanidins are obtained from seeds, vegetables, fruits and plants. Previous studies have demonstrated that proanthocyanidins are beneficial to human health due to few side effects and multiple biological activities, such as immunoregulation, antioxidation, anti-inflammation, anti-angiogenesis, anti-proliferation and anti-tumor effects (13-17). Growing evidence from clinical and experimental studies indicates that proanthocyanidins are predominantly safe and effective against diseases, such as inflammatory disorders, OS-associated diseases, vascular disorders and immune complaints. Proanthocyanidins function by regulating immune balance, attenuating OS damage and promoting vascular endothelial integrity (14,16,18,19). Additionally, proanthocyanidins modulate the abnormal metabolism of the body to control metabolic complaints and neoplastic disorders through suppressing lipid peroxidation (LPO) and inflammatory responses (20-22). However, reports scarcely focus on the possible efficacy of proanthocyanidins in the treatment of HSP. Given that HSP is an immune-mediated and OS-induced vasculitis and proanthocyanidins possess immunomodulatory and antioxidative properties, the present study hypothesizes that proanthocyanidins could be a treatment for HSP. Therefore, the evidence that suggests the potential efficacy of proanthocyanidins in treating HSP is reviewed and discussed in the present study.

## 2. Possible pathogenesis of HSP

As a multi-factorial disease, the etiology of HSP is diverse and complex and includes microbial infection, foods, drugs and malignant tumors. Reports suggest that immune imbalance and OS that induce IgA-mediated vessel injury are involved in the pathogenesis of HSP (23,24). The abnormal activation of TLRs (primarily TLR4) and the downstream pathways, are implicated in this process (25-29).

*Role of immune dysregulation in HSP.* Immune imbalance, especially T helper 2 (Th2) and Th17 overactivity, facilitates secretion of numerous chemokines and inflammatory cytokines (such as TNF-α, IL-1, IL-4, IL-6, IL-17 and cell adhesion factors) and promotes the migration of leukocytes to inflammatory sites, thus aggravating vascular inflammation and exacerbating HSP (28,30). Donadio *et al* (27) demonstrated that overactivation of TLRs (primarily TLR4) and elevated levels of adaptive immunity appear in patients with HSP; these promote an imbalance of the T cells and a release of inflammatory cytokines. As the downstream molecule of TLRs, NF-κB is required for the development of T cells and is involved in the activation of CD4+ T cells, particularly Th2 and Th17 cells (31). TLRs initially promote NF-κB translocation and activation by recruiting MyD88; TLRs combined with MyD88 employ the IL-1 receptor-associated kinase 1 (IRAK1) and IRAK4 to induce the activation of the transforming growth factor-β-activated kinase (TAK) complex, which causes autophosphorylation of TAK1. TAK1 promotes phosphorylation of IκBα by degrading the inhibitor κ-B kinase, which facilitates dissociation of IκBα from NF-κB and the production of the NF-κB complex (a dimer of p50 and p65) (32). The activated NF-κB then promotes T cells to produce activation-associated molecules, thereby activating and increasing naive T cells. Stimulated naive T cells differentiate into the effector subpopulations, such as Th1, Th2 and Th17. NF-κB, by combining with enhancer sites of IL-4 and simultaneously binding with NF of activated T cells, stimulates IL-4 that then further promotes Th2 development and activation. By contrast, NF-κB facilitate the growth and development of Th17 cells through enhances the secretion of Th17 directive signals such as IL-17a, IL-6, TNF-α and TGF-β, and stimulating the expression of major transcription factors of Th17 (RORγt and RORγ) alongside c-Rel of the Rel family. In addition, activated NF-κB suppresses the function of regulatory T (Treg) cells, followed by initiation of immune imbalance and the inflammatory response (29,33-36). Due to activation of TLRs, a number of aberrant alterations emerge in patients with HSP, including a high-proportion of Th17 cells, Th1/Th2 cell imbalance and Th2-dominant immune response, as well as decreased IFN-γ and IL-4 release. These alterations contribute to production of pro-inflammatory/inflammatory factors and adhesion molecules, recruitment of immune/inflammatory cells and amplification of the immune/inflammatory response (28,37,38). Consequently, overactivated T cells in turn release inflammatory factors, especially Th2-released cytokines, to accelerate the proliferation and differentiation of B cells that synthesize and secrete antibodies (IgA, IgG and IgM). Igs bind to corresponding receptors and activate complement components 3/4 to trigger OS and initiate inflammation, which leads to vessel wall destruction and HSP (39).

Decreased Treg cells aggravates HSP. Based on the origin and differentiation, Treg cells are classified into three subtypes: Thymus-derived (t), also termed natural Treg cells; peripheral (p) and inducible (i). The tTregs are generated in thymus, while pTregs and iTregs are induced in peripheral sites (40,41). It is generally considered that an immune and inflammation imbalance weakens the function of Treg cells, which promotes inflammatory reactions and exacerbates the disease (34,42). Levels of CD4+CD25+Foxp3+ Treg cells markedly decrease in

patients with HSP, whereas Th17 cell levels markedly increase; this imbalance of Th17/Treg promotes Treg cell dysfunction in HSP, amplifying inflammatory responses and destroying immune defense (35). Conversely, stable expression of Foxp3 induces Treg cells to produce anti-inflammatory factor IL-10, which inhibits the inflammatory response and maintains immune homeostasis. Furthermore, there is a decrease of follicular Treg cells in blood of pediatric patients with HSP, along with an increase in follicular Th cells; this imbalance leads to the overactivation of B cells, which then stimulate IgA production and inflammation (43).

As an antigen-antibody reaction, the inflammatory process mediated by IgA is the pathology of HSP. B cell-secreted IgA antibodies induce chemokine IL-8/leukotriene B4 (LTB4) production and promote chemotaxis/aggregation of neutrophils, which stimulates the inflammatory response and causes damage to endothelial cells (ECs) (44,45). Excessive numbers of IgA antibody interact with FcαRI (a prototypical IgA receptor) and bind to vascular ECs (VECs), thereby attracting neutrophils to migrate to the blood vessel wall in the presence of IL-8, in addition to eliciting ROS production and OS occurrence and membrane LPO) (46,47).

*Biomarkers derived from investigation of OS activation in HSP.* OS describes an imbalance where production of oxidative species exceeds the capacity of antioxidant defense systems. This then leads to macromolecular damage and redox homeostatic disorder. Free radical reaction is a widely recognized phenomenon that is greatly involved in macromolecular damage (48-51). The overproduction of oxygen radicals or oxides, including ROS [such as superoxide anion (O2-), hydrogen peroxide (H2O2), hydroxyl radical and singlet oxygen] and reactive nitrogen species [such as nitric oxide (NO), peroxynitrite anion and nitrite ion] (52,53), disturbs the equilibrium of the oxidant/antioxidant system. This imbalance creates OS that causes damage to the skin and VECs. As the primary contributor to OS, ROS production is triggered by exogenous factors [such as ultraviolet (UV) radiation, heavy metal ions, ozone, drugs or toxins] and endogenous factors including mitochondrial electron transport chain, membrane-bound NADPH oxidase isoforms 1-5 and endoplasmic reticulum. NADPH oxidases in particular are the primary source of ROS (53,54). The electrons generated by NADPH are transferred by an NADPH enzyme onto molecular oxygen that is reduced to O2•-. Superoxide dismutase (SOD) catalyzes O2-conversion into H2O2, and more ROS are formed (55-57).

Increasing evidence has supported OS as a promoter in the progression of vascular disorder, and in particular HSP (58-60). It has been revealed that OS often occurs in HSP, presenting as high levels of ROS and malondialdehyde (MDA) and low SOD levels and total antioxidant capacity. Serum MDA is an indicator of LPO, which increases in the active phase of HSP (massive purpura is seen on the skin and some patients experience abdominal and joint pain) and indirectly signifies the degree of VEC injury in patients with HSP (5,61,62). The dysfunction or damage of ECs impacts on the integrity of the vascular wall and the permeability of the vessel, which is attributed to the amount of OS (63-65). As a result, inflammatory cells adhere to the vessel wall to exacerbate damage of the vascular endothelium and deposit IgA at the vascular wall; these in turn promote the production of chemokines, accumulation/infiltration of inflammatory cells and injury of the vessel to exacerbate OS, thereby forming a positive feedback loop (66-68). Previous studies have reported higher levels of MDA in the serum of patients with HSP compared with levels in healthy individuals; MDA levels are highest in patients with renal or gastrointestinal involvement (21-23). Similar reports have indicated that the damage of ECs and aggravation of vascular inflammation frequently occur in the production of ROS from OS, while neutrophils in patients with HSP positively mediate oxygen radical production (61,69). Superfluous ROS destroy the antioxidant system and trigger OS, whereas the impaired antioxidant defense system aggravates the persistence of OS. This stimulates the release of diverse inflammatory factors and inflammatory reactions around the blood vessels. IL-1β, activated by TLRs, contributes to the HSP inflammatory reaction and is regulated by a biphasic redox response (70-72). The excess ROS and attenuated antioxidant defense stimulates the secretion of IL-1β, while IL-1β and cytokines involved in the inflammatory cascade response enhance the deposition of IgA on ECs (71,73). Conversely, damaged VECs and activated neutrophils produce large amounts of ROS, triggering the pathological and clinical manifestations of HSP (5,60,74).

The aforementioned processes are regulated by TLRs and downstream signaling pathways. Activating numerous inflammatory signals such as MyD88 and NF-κB, TLRs promote release of inflammatory mediators and the formation of immune complexes along with the overactivation of Th2/Th17 and the reduction of Treg cell populations and functional activity.

*TLRs involvement in the induction of HSP.* TLRs, belonging to a family of pattern recognition receptors, functionally recognize molecules that are associated with infection/tissue damage-associated molecules to trigger innate immunity and inflammation. The activation of TLRs promotes immune dysregulation, inflammatory responses and OS, thereby promoting vascular skin disorder (such as HSP) by stimulating TLR-mediated signaling pathways. TLRs comprise 13 members (TLR1-TLR13) (75,76). In all TLR members, the extracellular region is responsible for identifying the pathogen-associated molecular patterns (PAMPs) of the disease-causing microorganism, while the cytoplasmic region induces cellular immunological response (77). TLR4 localization on the cell surface is important in immune inflammatory disorders; it specifically recognizes the lipopolysaccharide (LPS) of pathogens and stimulates immune inflammatory reactions by activating adaptive immunity-associated genes, such as MyD88 (78).

TLR4-mediated signaling pathways in immune responses primarily contain two categories: MyD88- and TIR-domain-containing adapter-inducing interferon-β (TRIF)-dependent pathway. Trough interacting with the MyD88, TRIF or TLR4 pathway that promotes downstream signaling molecule (NF-κB or activator protein-1) participation in immune inflammation (79). By stimulating MyD88, TLR4 activates NF-κB, thereby triggering signal transduction cascades and activating immune cells. MyD88 is an adaptor molecule recruited by almost all TLRs (TLR3-TLR13) (80,81).

MyD88 has two domains, namely the TIR domain that interacts with the cognate domain in the cytoplasmic tails of TLRs and the death domain that binds to the corresponding domain of IRAK4. In the MyD88-dependent pathway, the signal pathway is exclusively activated by TLR4; signals are transmitted from TLR4 to MyD88, then to IRAK4; in the presence of phosphorylated IRAK1, IRAK4 activates TNF receptor-associated factor 6 and promotes NF-κB-dependent gene expression (82). NF-κB is activated after binding with TAK1 complex; activated NF-κB up-regulates the expression of pro-inflammatory factors (such as TNF-α and IL-1β) and increases the functional activities of NADPH oxidase and mitochondria. Both NADPH oxidase and mitochondria could promote the production of ROS, which touch off OS and inflammation, further contributing abnormal activation of Th17/Th2 cells, arresting Treg cell function and resulting in immune disturbance (25,28,83-85). Stimulated Th17 and Th2 cells generate chemokines and inflammatory cytokines to trigger the migration of neutrophils to inflammatory sites, thereby exacerbating vascular inflammation and facilitating HSP initiation (28,30).

HSP is caused by factors such as infection, drugs or tumors, which cause TLRs recognize PAMPs to activate the innate immunity. By binding to MyD88, TLR4 triggers signal transduction and stimulates the NF-κB signaling pathway, which promotes Th1/Th2 imbalance and release of pro-inflammatory mediators (25,74,83). These enhance B cell proliferation and differentiation, which contributes to IgA production and deposition on the vascular wall, as well as vascular endothelial damage (25,38). As a result, inflammatory cytokines are attracted to elicit ROS production and OS. Increased ROS in turn promotes TLR4 expression and the interplay between TLR4 and ROS stimulates the immuno-inflammatory response (47,68). The aforementioned molecular events cause further VEC injury and vascular permeability, ultimately leading to histopathological changes and clinical manifestations of HSP. The possible pathogenesis of HSP is presented in Fig. 1.

## 3. Biological properties and clinical applications of proanthocyanidins

Proanthocyanidins, a type of polyphenolic compound, are present in leaves, flowers, seeds, stems and roots, including common fruits and plants, such as grape, cranberry, black currant, pomegranate, cocoa and medlar (86). Proanthocyanidins comprise epicatechin, catechin, epigallocatechin or gallocatechin subunits connected by C4-C6 and C4-C8 bonds. Depending on the degree of polymerization, proanthocyanidins are primarily classified into two isoforms, namely oligomer proanthocyanidin (OPC) that have 2-5 monomers and polymer proanthocyanidin (PPC) that possess >5 monomers (87). Based on low molecular weight, OPCs exert prominent bioactivities such as immune modulatory, antioxidant, anti-inflammatory, antibacterial, anticarcinogenic, vascular protective and anti-hyperglycemic effects, which enable their application in clinical treatment (88-93). The bioactivity of PPCs is weaker due to the long carbon chain but increased by degeneration (94). Owing to their powerful immunomodulatory and antioxidant effects, proanthocyanidins are used to control immune-inflammatory and OS-associated disorder (95).

Previous studies have indicated that proanthocyanidins improving immune/inflammatory response and promoting lymphocyte transformation (96,97). Studies have confirmed that proanthocyanidins could modulate the balance of immune cells (especially T cells) and inflammatory cells to alleviate the immune/inflammatory reaction (96-99). Park *et al* (98) demonstrated *in vitro* and *in vivo* that proanthocyanidins notably increase gene transcription and protein levels of IFN-γ and decrease expression of IL-6. This results in activation of Th1 cells and inactivation of Th2 cells and a balance in humoral and cellular immunity. Furthermore, research on a murine model of auto-immune arthritis revealed that proanthocyanidins are effective in alleviating mouse arthritis symptoms by suppressing proliferation and differentiation of Th17 cells, increasing the activity and quantity of Treg cells and preventing secretion of various inflammatory cytokines, such as IL-17, IL-6, IL-21, IL-22 and TNF-α (96,99). Jhun *et al* (97) demonstrated that obesity and arthritis of both diet-induced obese mice and rheumatoid arthritis-like mice are relieved by proanthocyanidin treatment due to its ability to increase populations of the Treg cells and decrease the populations of the Th17 cells. Additionally, proanthocyanidins effectively prevent ovalbumin-induced allergic reactions by not only decreasing the release of inflammatory factors by regulating Th-derived cytokine expression (such as IL-4, IL-5 and IL-13), but also by inhibiting Ig (IgG1 and IgE) synthesis (100).

Furthermore, proanthocyanidins prevent OS, restore normal immune function and enhance antioxidant capacity by regulating multiple pathways, eliminating ROS/MDA, maintaining the balance of immune cells and inflammatory factors and upregulating detoxication enzyme and antioxidants (101-103). Kim *et al* (104) demonstrated that grape seed-derived proanthocyanidins effectively relieve joint swelling and the histopathological damage in a collagen-induced murine arthritis model through decreasing the levels of TLR4, MyD88 and NF-κB and inhibiting the TLR4/MyD88/NF-κB signaling pathway. Additionally, similar report has demonstrated that proanthocyanidins protectors against cisplatin-induced inflammatory and oxidative damage in the liver by suppressing TLR4/NF-κB (105). The proanthocyanidins not only down-regulate gene expression of TLR4 and NF-κB and decrease levels of inflammatory factors such as IL-1β, IL-6 and TNF-α, but also decrease the production of OS-associated mediators (such as ROS and MDA) and upregulate antioxidants [such as heme oxygenase-1 (HO-1), glutathione (GSH), SOD and catalase] (105). Proanthocyanidins minimize the formation of MDA and its metabolites by inhibiting the LPO process (106); proanthocyanidins could protect the function of ECs and minimize risk of vascular complications in diabetes by decreasing LPO and inhibiting OS (107). Outcomes from numerous studies have demonstrated that proanthocyanidins mitigates photo-oxidative damage to prevent UV-induced melanoma and other types of skin cancer by regulating T cells and inhibiting MAPK/NF-κB signaling pathways (19,108,109). Furthermore, proanthocyanidins decrease LPS-stimulated inflammation and OS by inhibiting inflammatory cytokines (TNF-α and IL-6) and controlling MAPK/NF-κB signaling pathways (102,110,111). Jia *et al* (112) demonstrated that

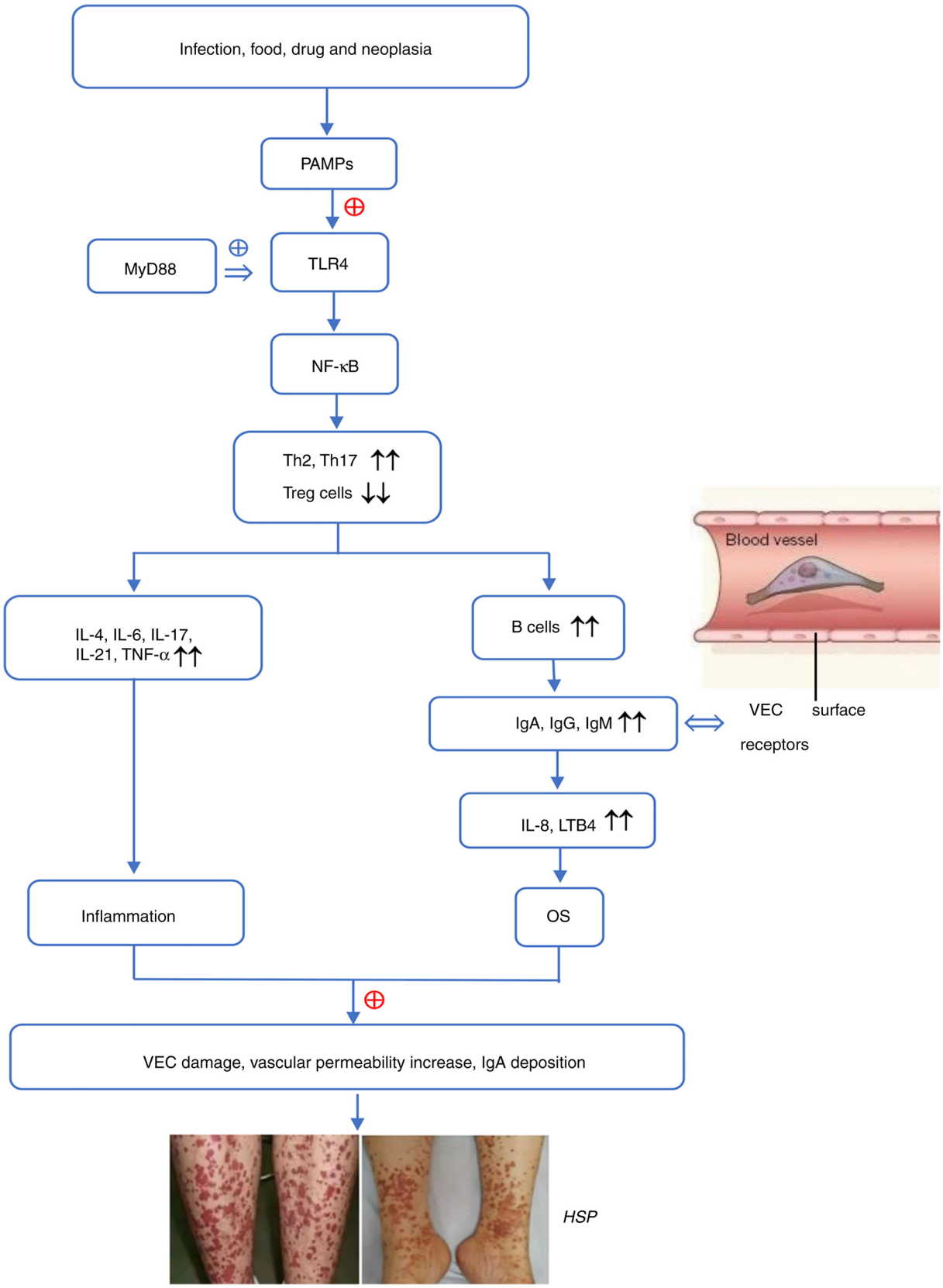


Figure 1. The possible pathogenesis of HSP. PAMPs are specifically recognized by TLRs. By binding to MyD88, activated TLR4 stimulates the downstream signaling molecule NF-κB to trigger signal transduction cascades and activate immune cells. Th1/Th2 imbalance and overactivated Th17 release inflammatory cytokines and also accelerate the proliferation and differentiation of B cells, which secrete antibodies. IgA may combine with VEC surface receptors to produce IL-8 and LTB4, which recruit neutrophils to the blood vessel wall and promote OS and inflammation due to downregulation of superoxide dismutase, total antioxidant capacity, glutathione and heme oxygenase-1 and the upregulation of reactive oxygen species, malondialdehyde, nitric oxide and inflammatory factors. These alterations leads to VEC damage, an increase in vascular permeability and IgA being deposited on the vascular wall, thereby contributing to the occurrence and progression of HSP. HSP, Henoch-Schonlein purpura; OS, oxidative stress; TLR4, toll-like receptor 4; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor κ-B; Th, T helper; IL, interleukin; TNF-α, tumor necrosis factor-α; Ig, immunoglobulin; LTB4, leukotriene B4; VEC, vascular endothelial cell; PAMP, pathogen-associated molecular pattern; Treg, regulatry T cell; , activation; ↔, binding; ↑↑, upregulation; ↓↓, downregulation.

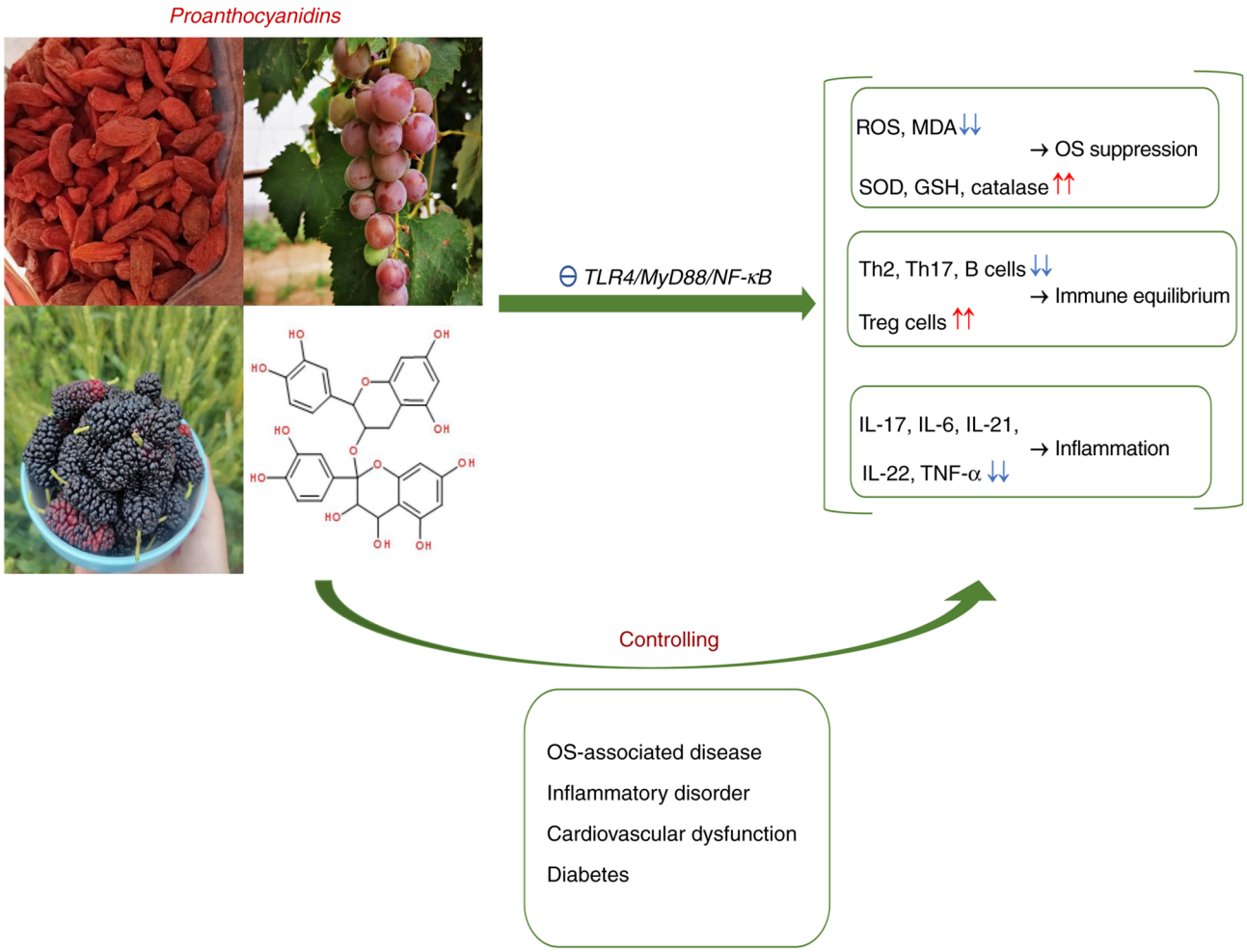


Figure 2. Proanthocyanidins structure, properties and application. Proanthocyanidins, a type of polyphenolic compound, are widespread in fruits and plants, such as grapes, cranberry, black currant, pomegranate, cocoa and medlar. Proanthocyanidins possess antioxidation, immunomodulation and anti-inflammation effects and are used in numerous disorders (such as OS-associated diseases inflammatory disorders, cardiovascular dysfunction and diabetes). Mechanism of action involves inhibiting OS (decreasing ROS and MDA and increasing SOD, GSH and catalase), reducing inflammatory responses (inhibiting IL-17, IL-6, IL-21, IL-22 and TNF-α) and balancing immunity (reducing Th2, Th17 and B cells and increasing Treg cells) via the suppression of the TLR4/MyD88/NF-κB signaling pathway. OS, oxidative stress; ROS, reactive oxygen species; MDA, malondialdehyde; TLR4, toll-like receptor 4; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor κ-B; Th, T helper; IL, interleukin; TNF-α, tumor necrosis factor-α; SOD, superoxide dismutase; GSH, glutathione; Θ, suppression; ↑↑, upregulation; ↓↓, downregulation.

suppression of NF-κB by proanthocyanidins facilitates protect human lens epithelial B-3 cells from oxidative damage and inflammatory injury. Proanthocyanidins could reduce $H_2O2$-induced OS damage and delay cataracts occurrence by inhibiting activation of NF-κB and MAPK pathways. In a previous study, proanthocyanidins were demonstrated to inhibit production of iNOS, which is key to lower NO levels, indicating the antioxidant ability of proanthocyanidins (110). Proanthocyanidins exerted a protective effect in the animal model of gingivitis with porphyromonas gingivalis infection via reducing the release of IL-1β, IL-6, ROS, NO and lipid peroxide, thereby inhibiting alveolar bone loss (91,113). Due to their potent antioxidant and anti-inflammatory capacities, proanthocyanidins enhance the function of VECs and maintain blood pressure stability by inhibiting inflammatory cytokine production (74). Proanthocyanidins protect VECs from OS damage through inhibiting NADPH oxidase activity and scavenging excess ROS (114,115). Pinna *et al* (116) demonstrated that proanthocyanidins prevent vascular endothelial damage in diabetic rats by serving as a strong ROS scavenger. Proanthocyanidins similarly attenuate OS and inflammatory responses by eliminating ROS and inhibiting NF-κB gene expression, thus decreasing capillary permeability and maintaining vascular homeostasis (117).

A number of clinical trials has verified that proanthocyanidins are a pharmacologically safe and effective agent without negative effects and are suitable for a range of populations, including pregnant people (118,119). Proanthocyanidins reliably relieve symptoms of patients that suffered from urinary tract infections or gingivitis (91,120). However, an *in vivo* study in female rats, reported that high-dose proanthocyanidin (>432 mg/kg) could cause delayed gastric emptying and pica behavior (121). At present, to the best of our knowledge, extensive research of proanthocyanidins has been performed in various disorders but reports regarding HSP are rare (91,105,109,122). Fig. 2 presents the molecular structure and multi-bioactivity of proanthocyanidins as well as their application in different types of disease.

## 4. Hypothesis of proanthocyanidins in the management of HSP

As immune imbalance and OS-induced IgA mediated vessel injury are implicated in HSP and proanthocyanidins have immunoregulatory, antioxidant and anti-inflammatory activity, it is hypothesized that proanthocyanidins may be beneficial to patients with HSP. HSP is a recurrent, immune-mediated vasculitis that invades arterioles and capillaries, typically featuring IgA deposition along vascular walls (23,45,46,123); immune imbalance and OS are responsible for HSP pathogenesis and involve signals from TLR4 and its downstream pathways MyD88/NF-κB (5,23,46,61,62); high proportions of Th2/Th1 as well as Th17/Treg and Th2 and Th17 overactivation are associated with increased ROS and redox imbalance in lesions and blood samples from patients with HSP; furthermore, Th2/Th17 promotion of Ig (primarily IgA) production and deposition are frequently observed in patients with HSP. The aforementioned factors stimulate and maintain the progression of HSP and, therefore may serve as potential targets for treatment of HSP (26,27,62,124). The aforementioned events are mediated by the TLR4/MyD88/NF-κB signaling pathway and a number of studies demonstrated high levels of TLR4 in patients with HSP accompanied by an increase in MyD88 and NF-κB, followed by release of inflammatory factors (such as IL-4, IL-6, IL-8, IL-17, IL-21 and LTB4) (5,25-29). Proanthocyanidins mitigate inflammatory and oxidative damage in inflammation/OS-associated disorder by inhibiting TLR4/MyD88/NF-κB pathways and inflammatory factors (IL-1β, IL-6 and TNF-α), scavenging NO, ROS and MDA and increasing release of HO-1, GSH, SOD and catalase (18,89,102,104,105,125). Proanthocyanidins improve vascular endothelial function, decrease vascular permeability and prevent vascular damage by inhibiting release of inflammatory factors, eliminating ROS and reducing the production of Igs and deposition of immune complexes (92,116,117,126). Thus, proanthocyanidins are currently applied in immune-mediated and vascular disorders to improving vascular endothelial function in hypertensive patients (92). The aforementioned hypothetical mechanisms of proanthocyanidins in treating HSP are based on inactivation of the TLR4/MyD88/NF-κB pathways, inhibition of OS, suppression of inflammation and balance of immunity (Fig. 3).

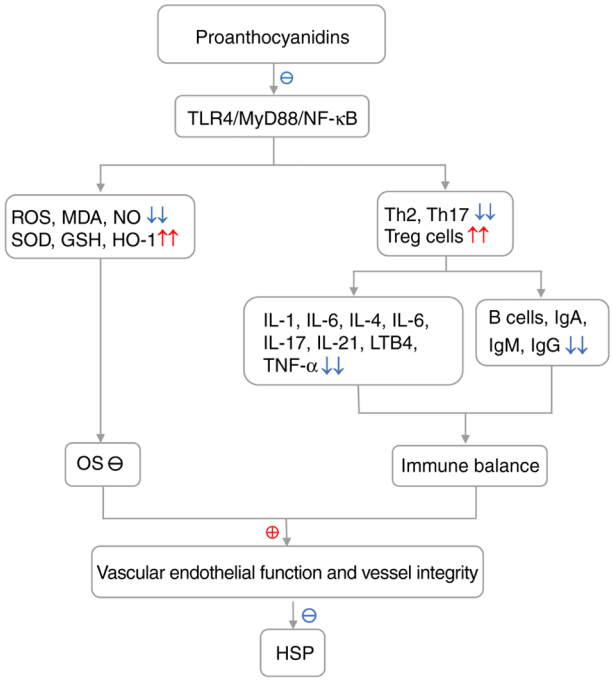


Figure 3. Potential mechanisms of proanthocyanidins in treatment of HSP. Proanthocyanidins inhibit TLR4/MyD88/NF-κB signaling to arrest OS by eliminating oxidants such as ROS, MDA and NO, accompanied by an increase of antioxidants, such as HO-1, SOD and GSH. By inhibiting the TLR4/MyD88/NF-κB pathway, proanthocyanidins cause a decrease in Th2/Th17 cells and an increase in the Treg cells, which inhibits release of inflammatory factors (IL-1, IL-6, IL-4, IL-6, IL-17, IL-21, LTB4 and TNF-α), activation of B cells and antibody production, facilitating immune homeostasis. The aforementioned alterations improve the vascular endothelial function and vessel integrity, thereby potentially contributing to control of HSP. HSP, Henoch-Schonlein purpura; TLR4, toll-like receptor 4; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor κ-B; OS, oxidative stress; ROS, reactive oxygen species; MDA, malondialdehyde; NO, nitric oxide; HO-1, heme oxygenase-1; SOD, superoxide dismutase; GSH, glutathione; Th, T helper; Treg, regulatory T cell; IL, interleukin; TNF-α, tumor necrosis factor-α; Ig, immunoglobulin; Θ, suppression; □, improvement; ↑↑, upregulation; ↓↓, downregulation.

## 5. Clinical significance

As the most common form of systemic vasculitis in children, annual incidence rate is up to ~27/100,000 (127). HSP presents as a skin impairment; multi-systemic involvement, which can be life threatening, is a research focus. Despite conventional medications to control HSP, such as anti-inflammatory drugs, corticosteroids, cytotoxic drugs and immunosuppressants (8,127,128). These measures are unsuitable for long-term use due to the high cost, transient efficacy and severe adverse effects, like long-term and large-scale use of glucocorticoids could cause infections and Cushing's syndrome; long-term use of cytotoxic drugs that could result in gastrointestinal reactions, hepatotoxicity, bone marrow suppression, reproductive toxicity, cardiotoxicity (12). Proanthocyanidins, as natural extracts from plants, have widespread sources and diverse bioactivity with minimal side effects and can be used by pregnant people (118). Therefore, proanthocyanidins are preferable options for treatment of HSP based on their immunoregulatory, antioxidant and anti-inflammatory properties and may prevent OS-induced damage and modulate immune balance by scavenging ROS, maintaining Th1/Th2 and Th17/Treg balance and decreasing the secretion of inflammatory factors by the inhibition of TLR4/MyD88/NF-κB signaling pathways (99,102,104). In addition, a number of factors may affect the efficacy of proanthocyanidins in treatment of patients with HSP, such as dose of medication, the duration of drug intervention, the quality of the experimental models (Models with insignificant pathological manifestations or molecular biological alterations could affect the judgement of the efficacy of proanthocyanidins), the physical status of patients and the presence of underlying pathological conditions.

## 6. Future research

Future research should evaluate the effects of proanthocyanidins on HSP-associated clinical manifestations, histopathological or immunopathological alterations,

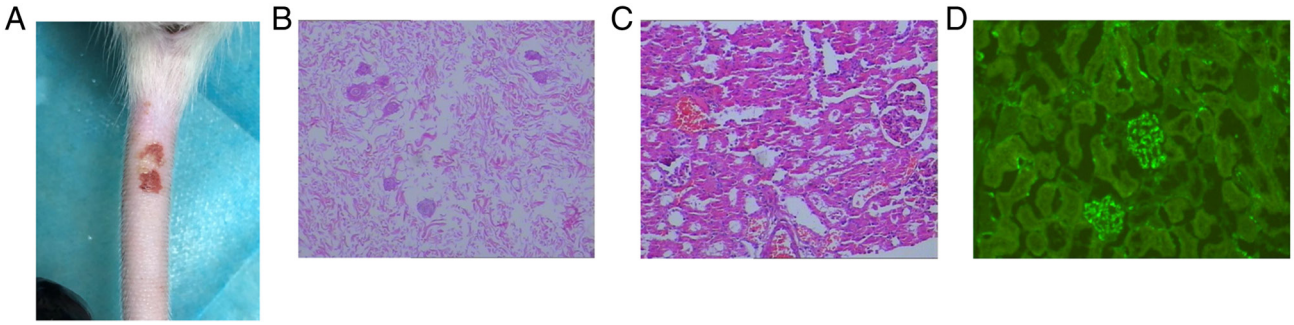


Figure 4. Establishment of HSP-like rat models. (A) Cutaneous eruption on the tail of a HSP-like mouse model demonstrating a typical purpura-like lesions on the skin. (B) Histopathological changes of skin of HSP-like rat models revealing leukocytoclastic vasculitis accompanied by edema in dermis and fibrinoid degeneration on the vascular walls in the upper dermal layer. (C) Histopathological alterations of the kidney of a HSP-like mouse model revealing proliferation of mesangial cells/stroma with protein exudation and scattered hemorrhage in renal tissue. (D) Immunofluorescence of the kidney of the HSP-like mouse model revealing granular deposition of IgA. HSP, Henoch-Schonlein purpura.

cytological and serological changes such as cutaneous or systemic symptoms, VEC swelling, fibrin degeneration/necrosis, inflammatory cell infiltration, IgA deposition along vascular walls, T/B cell quantities and inflammatory/OS-associated indicator levels, in the presence or absence of proanthocyanidins. The present study assumes that proanthocyanidins would be beneficial for HSP. Therefore, to verify this hypothesis and reveal the effectiveness of proanthocyanidins in the treatment of patients with HSP, animal experiments *in vivo* should be performed to evaluate the effects of proanthocyanidins in well-established HSP-like rats models (129). The present review describes the successful construction of HSP rat models based on the model research of Li *et al* (130). In the aforementioned study, Sprague Dawley rats were intraperitoneally injected with ovalbumin (OVA) emulsified solution (1:1 OVA solution mixed with Freund's Complete Adjuvant) once/week for 3 weeks. After 3 weeks, rats were injected with 1 ml 10 mg/ml OVA saline via the tail vein, and intradermal injection of 1 ml 0.3% saline to stimulate hypersensitivity type III; finally, a rat model of HSP was successfully built. The preliminary results indicated the skin of the abdomen and tail of the rats visually presented with scattered petechiae and ecchymosis; histopathology of the skin revealed subcutaneous hemorrhage and inflammatory infiltration; renal histopathology revealed mesangial cell and matrix proliferation and immunofluorescence of renal tissue exhibited granular deposition of IgA immune complexes in the mesangial area (Fig. 4) (129). Additionally, *in vitro* studies using HSP-like cell models should be performed to investigate the mechanism of proanthocyanidins in HSP. Furthermore, updated biological techniques should be used to determine the associated parameters. In addition, randomized placebo-controlled clinical trials may establish a scientific basis for further research and clinical application of proanthocyanidins.

## 7. Conclusion

HSP, an IgA-mediated vasculitis, commonly affects children, affects the skin and systemic organs and threatens life. The etiology and pathogenesis of HSP are unclear but currently it is hypothesized to be a multifactorial disorder involving immune imbalance, OS, infection, genes, foods, drugs and complex cytokine networks (23,27,124). Immune dysregulation and OS that induce IgA-mediated vascular injury are responsible for HSP and involve abnormal activation of TLR4/MyD88/NF-κB signaling. Thus, targeting these areas could lead to a treatment for patients with HSP. Treatments, such as targeting key inflammatory mediators, pathways or cells, have exhibited positive effects on HSP (5,131). Typically, corticosteroids have greater efficacy on severe cutaneous and visceral involvement such as gastrointestinal or kidney impairment by suppressing T/B cell activation, antibody production and inflammatory factor release (132-134); for example, patients with severe purpura nephritis are treated with methylprednisolone pulse therapy that effectively reduces kidney pathological injury and shortens treatment course (135). However, glucocorticoids merely ease the symptoms, while excessive use of glucocorticoids may lead to gastrointestinal bleeding or electrolyte disturbance (136,137). Furthermore, because of susceptibility to resistance to glucocorticoid treatment alone, the combination of glucocorticoids with an immunosuppressant tends to be more effective and safer, especially for patients with severe HSP nephritis (137,138); immunosuppressive agents such as mycophenolate mofetil act against purpura nephritis via selectively suppressing T/B lymphocytes (139). Additionally, plasma exchange has a notable effect on patients with recurrent or acute HSP by improving renal function and clearing immune complexes (140). Despite these treatments having efficacy against HSP, adverse reactions, short-term efficacy and high cost prevent widespread use. Therefore, safe, effective and cheaper treatments are needed for HSP. The present study explained the pathogenesis of HSP and applications of proanthocyanidins in clinical practice. Proanthocyanidins have potential as therapy of HSP, although factors, such as the dose of drug, the duration of drug intervention, quality of experimental models and patient's physical condition may affect proanthocyanidins for HSP treatment. Thus, the aforementioned factors should be investigated in future research. Additionally, studies *in vitro* and *in vivo* should be performed to verify the signaling pathways in HSP and to identify improvements in diagnostic biomarkers following proanthocyanidin treatment.

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**Availability of data and materials**

Not applicable.

**Authors' contributions**

QD revised the manuscript. MG conceived the study. XL and YX wrote the manuscript. YX, JZ and DX performed the literature review. Data authentication is not applicable. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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