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REVIEW ARTICLE

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Research progress on icariin, a traditional Chinese medicine extract, in the treatment of asthma

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ABSTRACT
Bronchial asthma is a common chronic airway disease, and long-term management of asthma is the focus and challenge of clinical treatment. Glucocorticoids are often used as the first choice for the treatment of asthma. However, the occurrence of hormone dependence, hormone resistance, and local and systemic adverse reactions caused by hormone application also creates problems for the treatment of asthma. Finding new, safe, and effective therapeutic drugs is an important research direction at present. Icariin is an effective ingredient of the traditional Chinese medicine, Epimedium. It has various biological attributes such as anti-inflammatory and antioxidative activities, and immune regulation. It has high safety and a wide range of clinical applications. Icariin has the characteristics of multitargeted intervention in the treatment of asthma. Here, we review the specific mechanisms of icariin in treating asthma, and icariin is considered a novel therapy in controlling asthma; however, the mechanism is still worth further investigation.

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Introduction

Bronchial asthma (asthma) is a group of highly heterogeneous chronic airway diseases with different pathogeneses and various clinical manifestations. The main manifestations are cough, chest tightness, dyspnea, wheezing, and other symptoms.[1] Chronic airway inflammation and airway remodeling are key features of the onset of asthma, and they can lead to airway hyperresponsiveness and restricted lung function.[2] There are various classifications of asthma. According to its pathogenesis, it can usually be divided into Th2-related asthma and non-Th2-related asthma. The former is mainly characterized by increased airway eosinophils, while the latter mostly manifests as increased airway neutrophils.[3,4] At present, there are approximately 300 million asthma patients in the world, and on average, more than 1,000 people die of asthma every day.[5] Inhaled corticosteroids (ICSs) are currently recognized as the main treatment for asthma, but approximately 30%–50% of asthma patients still receive hormone therapy, and hormone dependence and multiple side effects caused by hormone use cause difficulties in the long-term management of asthma.[6]

Traditional Chinese medicine has a history of thousands of years in treating asthma, and it was recorded in the "Treatise on Febrile and Miscellaneous Diseases" written by Zhang Zhongjing of the Eastern Han Dynasty.[7] Various traditional Chinese medicines and their extracts have been found to have a significant therapeutic effect in the treatment of asthma in modern medicine, and presently this is an important research direction for asthma treatment. In recent years, many new research advances have been made on the specific mechanism of action of icariin in the treatment of asthma, and they are summarized as follows.

Icariin

The source of icariin

Epimedium pubescens (*Epimedium pubescens Maxim*), is also known as *barren grass*. It has three branches on the stem and three leaves in each branch, and it is also called the three-branched, nine-leafed clover. It mainly grows on cliffs near moist forests, streams, and wetlands at altitudes of 200 to 3700 m. It is a perennial temperate and subtropical medicinal plant belonging to the Berberis family.[8] *Herba Epimedii* is the dry leaf of the Epimedium plant. The classic Chinese medicine literature, "Shen Nong's Materia Medica" recorded more than 400 years ago that *Herba Epimedii* has the effects of "tonifying kidney yang," "strengthening muscles and bones," and "dispelling rheumatism."[9] Modern studies have found that Epimedium and its extracts have a certain therapeutic effect on improving osteoporosis, asthma, and cardiovascular diseases, and have been widely used in clinical treatment in China, South Korea, Japan, and other East Asian countries.[10-13]

The molecular structure and biological activity of icariin

The molecular formula for icariin (2-(4′-methoxylphenyl)-3-rhamnosido-5-hydroxyl-7-glucosido-8-(3′-methyl-2-butylenyl))-4-chromanone, ICA), is C33H40O15, and its molecular weight is 676.67. It is a pentenylated flavonoid glycoside monomer extracted from the traditional Chinese medicine, Epimedium, and it is one of the most important pharmacologically active ingredients in Epimedium.[14] It has multiple effects such as regulating immunity, exerting anti-inflammatory and antioxidative activities, inhibiting cell apoptosis, and improving endothelial cell function.[15] Icariin mainly acts in the body through its metabolites. The main absorption site of icariin is in the small intestine. It can be quickly converted into icariin II (deglucosyl) and absorbed into the blood in the intestine. Bile is in the form of icariin 3-OL-rhamnopyranosyl-7-OD-glucopyranoside. Icariin II that enters the body can regenerate C7-OH glucoaldehydation in the liver.[16]

A clinical trial of icariin and mood and alcohol use disorders demonstrated that icariin not only effectively improves mood and alcohol use disorders in patients but also is highly safe and well tolerated.[17] Icariin has received widespread attention in clinical treatment due to its wide-ranging effects. In research on lung cancer treatment, icariin was found to target the PI3K-Akt signaling pathway; reduce the phosphorylation levels of Bax, Bad, and other factors; and reduce the mitochondrial membrane potential to promote tumor cell apoptosis.[18] In the treatment of myocardial damage and heart failure, icariin, as a flavonoid compound, exhibits a strong ability to resist oxidative stress.[19] Icariin can also combine with inorganic materials such as hydroxyapatite to form a new type of drug scaffold that can effectively promote bone damage repair.[20]

The Mechanism of Action of Icariin in the Treatment of Asthma

The mechanism of icariin in inhibiting airway inflammation (Table 1)

Icariin could regulate the expression of eosinophils and basophils

Eosinophils (EOS) are considered key cells and treatment target in asthma, and the eosinophil count is closely related to asthma symptom control.[21] Further studies have shown that eosinophils can express leukotriene hydrolase A4 (LTA4H) and generate LTB4, which can enhance asthma inflammation.[22] Basophils (Bas) were also identified to generate IL-4 to affect the function of ILC2s in lung inflammation and may act as a potential biomarker.[23] BuShenYiQi is a traditional Chinese herbal formula in which *Herba Epimedii* has been confirmed as one of the main components by high-performance liquid chromatography (HPLC). In the model of RSV-induced asthmatic rats, BuShenYiQi formula (BSYQF) showed a significant effect in reducing excessive infiltration of eosinophils and neutrophils, regulating the balance between Th1 and Th2/Th17 responses to inhibit asthma exacerbation.[24] BSYQF also inhibits the expression of inflammatory cells such as neutrophils (Neu), lymphocytes (Lym), monocytes (Mon), and basophils; enhances Tregs; and inhibits Th17 cells function to reduce asthma inflammation.[25] Further studies have found that icariin may affect the chemotactic migration of EOS to effectively

Table 1 The mechanism of icariin in inhibiting airway inflammation to treat asthma.

No	Extract/ monomer	Patients/ animal/cell	Dose	Possible mechanism/function	Reference
1	Bu-Shen-Yi-Qi formula ((BSYQF)	Mice	2.5, 5, and 10 g/kg/ day, po.; for 15 days	BSYQF could effectively improve the inflammatory cells' infiltration such as eosinophils in asthma, and to regulate Th1 and Th2/Th17 balance.	[24]
2	BSYQF	Mice	5, 10, and 20 g raw herbs/kg body weight, po., for 8 weeks	BSYQF could reduce the differentiation of Th17 and improve the enhancement of Treg functions to regulate Th17/Treg imbalance in asthma treatment.	[25]
3	Icariin	Mice	5, 50, and 100 mg/ kg/2 days, ip.; for 6 weeks	Icariin could downregulate the expression of Bcl-2 and upregulate the expression of Bax protein, promote the apoptosis of EOS in asthmatic mice, and reduce the EOS infiltration.	[26]
4	Icariin	Mice	40 μg/single injection/mouse, ip., for day 1 and day 22	Icariin may act as a safe adjuvant in mice and be able to induce both Th1 and Th2 responses.	[30]
5	Icariin	Rat	5 mg/kg; 10 mg/kg; 20 mg/kg, ig., for 2 weeks	Icariin was found to reduce the inflammatory cell infiltration in rat asthmatic bronchi, under the vessel mucosa and in peripheral tissue, with targeting p65 protein to inhibit the differentiation of eosinophile granulocyte and macrophage.	[31]
6	Icariin	Mice	25 mg/kg, 50 mg/kg, 100 mg/kg, po., for 8 weeks	Icariin was found to reduce airway inflammation by reducing the expression of IL-6, IL-17, TGF-β, and inhibiting Th17 functions while improving the enhancement of Treg functions.	[34]
7	Icariin	HeLa and RAW 264.7 cells	Three concentrations (7.5 μM, 15 μM, and 30 μM) for 24 h	Icariin was able to enhance the functions of glucocorticoids (GCs) and promote glucocorticoid receptor (GRα) translocate into the nucleus with targeting the NF-κB and STAT3 to reduce LPS-induced inflammation.	[39]
8	Fructus Ligustrilucidi extracts; Herbal Epimedii extracts	Rat	100 mg/kg, ig., for 4 weeks	This study showed that co-combination of HE and FLL seemed to have stronger effects in antioxidant and regulating immunity than single use of extracts with targeting TGF-β/Smads signaling; besides, two extracts combined with budesonide expressed the best effects in regulating the expression of TGF-β1, 2, and Smad2,3 and Smad7 to treat asthma.	[40]
9	Icariin	Mice	2.5 mg/200 μl normal saline once a week, ip., for 2 weeks	Icariin can downregulate the expression of prostaglandin D2 (PGD2) and prostaglandin D2 receptor 2 (CRTH2) to reduce the chemotaxis of eosinophils and to improve Th17/Treg imbalance in asthma.	[43]
10	Suhuang antitussive capsule	Rat	1.75, 3.5, and 7 g/kg, ig., for 2 weeks	Suhuang may regulate TXNIP induction and RIP1-RIP3-DRP1 signaling to inhibit the activation of NLRP3 inflammasome and attenuate endoplasmic reticulum stress to improve pulmonary dysfunction.	[44]
11	Icariin	Primary hippocampal neurons of rat	10, 20, and 50 nM, for 2 h	It was identified that icariin could attenuate CRH-induced ER stress and apoptosis, targeting to upregulate the activation of NF-kB.	[46]

ip.: Intraperitoneal Injections; Th: T helper type; ig.: Oral administration; BSYQF: Bu-Shen-Yi-Qi formula; p.o.: per os; Treg: Regulatory cells; GCs: Glucocorticoids; GRα: Glucocorticoid receptor; IL: Interleukin; TGF-β: Transforming growth factor-β; NF-κB: Nuclear factor kappa-B; STAT: Signal transducer and activator of transcription; LPS: Lipopolysaccharide; FLL: *Fructus Ligustrilucidi*; HE: *Herbal Epimedii*; PGD2: Prostaglandin D2; CRTH2: Prostaglandin D2 receptor 2; TXNIP: Thioredoxin-interacting protein; RIP: Receptor-interacting protein; DRP: Dystrophin-related protein; NLRP3: NOD-like receptor family, pyrin domain containing 3; CRH: Corticotropin releasing hormone; ER: Endoplasmic reticulum.

reduce inflammation in asthma by downregulating the expression of chemokines RANTES and McP-3 in lung and CCR3 and eotaxin on EOS surfaces, inhibiting the expression of bcl-2, which is an anti-apoptotic protein.[26]

Icariin could improve Th1/Th2 cell imbalance

The occurrence and development of asthma is closely related to the participation of a variety of immune cells. Initial CD4+T cells (naive CD4+T Cells) can be differentiated into a subgroup of T helper (Th) cells with diverse functions, among which T helper 2 cells (Th2) are the main response cells for asthma.[27] Studies have found that under the stimulation of allergens, Th2 cell subtype differentiation is enhanced and Th1 cell differentiation is inhibited, which leads to an imbalance of Th1/Th2 cells and causes corresponding inflammation.[28] Further studies have shown that GATA3 is the main transcription factor involved in Th2 cell differentiation induction, while T-bet and Runx3 mainly control Th1 cell differentiation.[29] Some scholars have found that icariin has the immunomodulatory effect of enhancing the Th1-related immune response in rats and inhibiting Th2 cell differentiation.[30] In addition, by comparing the expression of corresponding transcription factors in the lung tissues of the rat asthma group and the icariin treatment group, icariin intervention was found to significantly downregulate the expression levels of GATA3 and T-bet, thereby inhibiting Th2 cell differentiation and regulating Th1/Th2 cell imbalance to improve asthma airway inflammation.[31]

Icariin could improve the imbalance of Th17/Treg cells

Regulatory T cells (Tregs) are CD4+T cells that are critical to the development and homeostasis of Th2 cells.[32] The decrease in Treg cells and the increase in the number of Th17 cells in asthma patients are important pathogenic mechanisms of asthma and one of the main research directions for clinical treatment.[33] Experiments by Ying Wei et al. suggest that the traditional Chinese medicines *Epimedium and Astragalus* may play an important role in inhibiting TH17-related inflammatory factors, such as IL-6 and IL-10, and promoting Treg cell-related factors such as FOXP3, providing a new treatment direction to improve the imbalanced ratio of TH17/Treg cells in asthma.[25] Further studies have found that IL-6 can combine with TGF-β to promote Th17 differentiation and inhibit Treg cell function, and in an ovalbumin-induced asthma model, icariin was confirmed to effectively inhibit the expression of IL-6, IL-17, TGF-β, and other inflammatory factors to promote FOXP3 expression and Treg cell development and differentiation, significantly improving TH17/Treg cell imbalance and relieving asthma airway hyperresponsiveness and airway inflammation.[34]

Icariin could regulate the hypothalamic-pituitary-adrenal axis (HPAA)

Hypothalamic–pituitary–adrenal axis dysfunction often occurs in patients with chronic asthma, which affects Th1/Th2 cell imbalance, promotes the secretion of inflammatory factors mediated by eosinophils and TH2 cells, and further promotes airway inflammation, and it is also an important mechanism in asthma treatment.[35] Glucocorticoids (GCs) can bind to glucocorticoid receptors (GRs) to inhibit or activate the transcription of genes in the nucleus. GRα is the main mediating receptor that can inhibit nuclear factor kappa-B (NF-κB), signal transducer and activator of transcription (STAT) family, and other inflammatory factors to exert a strong anti-inflammatory effect in vivo, whereas GRβ mainly plays a negative regulatory role.[36] However, steroid-resistance commonly occurs in asthma patients, especially in severe asthma patients.[37] Traditional Chinese medicine has been found to have potential synergistic effects on enhancing the effects of GC. In an in vitro experiment with HaCaT keratinocytes, icariin was found to inhibit the expression of IL-8 and IL-1b to reduce the inflammatory response. Pretreatment with icariin was also able to promote the activation of GC, and it showed a potential effect in improving insufficient GC secretion in chronic inflammation.[38] Icariin can significantly inhibit lipopolysaccharide (LPS)-induced cell inflammation, downregulate the expression of inflammatory factors such as NF-κB, AP-1, and STAT3, and partially restore the expression of GRα to decrease GC-resistance.[39] Tang Xiufeng et al. demonstrated that combining the extracts of *Herba Epimedii* (HE) and *Fructus Ligustri Lucidi* (FLL) with GC to treat asthma may result in much more efficient treating power, more obviously inhibiting the expression of TGF-β and improving airway remolding in asthma than the single use of GC.[40]

Icariin could inhibit the expression of prostaglandin D2 (PGD2)

In comparing the sputum and bronchoalveolar lavage fluid (BALF) of asthma patients and healthy people, the level of proinflammatory eicosanoids such as prostaglandin D2 (PGD2) was found to be significantly increased, and this is closely related to the severity of asthma.[41] PGD2 is mainly derived from activated mast cells, which can promote bronchoconstriction and activate and recruit a large number of TH2 cells by binding to the TP1 receptor and DP2 receptor (also known as CRTH2), and has become an important intervention target in the treatment of asthma.[42] Research conducted by J. Qiao et al. showed that icariin intervention can significantly downregulate the expression levels of PGD2 and CRTH2 in asthmatic mice, thereby effectively improving airway inflammation and airway remodeling.[43]

Icariin could inhibit endoplasmic reticulum (ER) stress

The endoplasmic reticulum is a multifunctional organelle of eukaryotic cells, and it plays an important role in protein modification, folding, and biosynthesis. Studies have shown that endoplasmic reticulum stress can increase the occurrence of inflammation and lead to chronic respiratory diseases.[44] In asthma, phosphoinositol 3-kinase (PI3K) is overactivated under the activation of TOLL-like receptors, leading to the accumulation of a large number of misfolded

proteins and reactive oxygen species (ROS), and cell endoplasmic reticulum dysfunction, stimulating the unfolded protein response (UPR), aggravating endoplasmic reticulum stress, airway inflammation, and airway remodeling processes.[45] In a model of primary cultured fetal rat hippocampal neurons, icariin not only obviously inhibited the corticotropin-releasing hormone (CRH)-induced ER stress and cell apoptosis but also reduced the activation of NF-κB; in addition, in an in vivo model of OVA_{LPS}-OVA-induced asthmatic rats, icariin treatment also showed a strong protective effect, inhibiting ER stress and the expression of the NF-kB pathway, and reducing airway hyperresponsiveness (AHR) in asthmatic rats to protect against ER stress and inflammation.[46]

The mechanism of icariin in inhibiting airway remodeling (Table 2)

Icariin could inhibit extracellular matrix (ECM) deposition

Airway chronic inflammation can lead to airway remodeling and promote asthma exacerbation, of which extracellular matrix deposition is one of the main manifestations of airway remodeling.[47] Transforming growth factor-1 (TGF-β1) is the main regulator that can promote airway fibrosis and collagen deposition by regulating cytokines such as Smads proteins.[48] In the treatment of diabetic nephropathy, icariin has been shown to exert antioxidative activity and inhibit extracellular matrix deposition.[49] In addition, *Herba Epimedii* (HE) and *Fructus Ligustri Lucidi* (FLL) combined with GCs were demonstrated to clearly improve collagen synthesis in respiratory epithelium in asthma model in rats, and the single GC treatment did not show the same effect; the combined treating was also found to reduce the expression of TGF-β1,TGF-β2,Smad2 and Smad3, and promote the expression of Smad7; this may be the main mechanism in improving ECM in asthma.[40]

Icariin could inhibit airway epithelial cell-to-mesenchymal transition (EMT)

In the process of airway remodeling, there is a phenotypic transformation of airway epithelial cells to mesenchymal morphology, including E-cadherin reduction and an increase in N-calcium expression, which can lead to a decrease in glucocorticoid sensitivity and severely affect the prognosis.[50,51] Studies have shown that TGF-β1 can regulate the miR-203a-3p/SIX1 signaling pathway to regulate the Smad3 pathway and promote the occurrence of epithelial-mesenchymal transition in asthma.[52] In vivo and in vitro experiments have found that icariin can significantly inhibit the phosphorylation of cytokines such as Erk, JNK, and p38; inhibit the activation of Smad and MAPK signaling pathways; and reduce the EMT process induced by TGF-β1 to improve airway remodeling.[53]

Table 2 The mechanism of icariin in improving airway remolding to treat asthma.

NO	Extract/ monomer	Patients/ animal/cell	Dose	Possible mechanism/function	Reference
1	Icariin	Rat	20, 40, 80 mg/kg, i.g., for 9 weeks	Icariin could reduce the expression of ROS and extracellular matrix deposition partly by influencing p62- Keap1 and Nrf2 signaling.	[49]
2	Icariin	Human bronchial epithelial cell line 16HBE; mice	16HBE cells: 25 mg/mL; 50 mg/mL; 100 mg/mL; for 6h; Mice: 25 mg/mL; 50 mg/mL; 100 mg/mL; ip., three times a week, for 6 weeks	Icariin was identified to attenuate TGF-β-Smads and MAPK signaling to reduce airway remolding; besides, the expression of N-cadherin and α-SMA was also inhibited and E-cadherin was downregulated both in 16HBE and asthma mice.	[53]
3	Icariin	Rat ASMCs	25 μM, 50 μM, 75 μM, 100 μM, 150 μM, 200 μM, 250 μM, and 300 μM, for 24 h, 48 h, and 72 h	Icariin was able to induce S phase acceleration and G2/M phase arrest regulate in ASMCs proliferation in a dose-dependent manner, which may be closely related to caspase pathway.	[55]
4	Icariin	Mice; ASMC	Mice: 25, 50, and 100 mg/kg, po., for 28 days; ASMC: 5, 10, or 100 μM for 24 h	ICA was found to improve the OVA-induced airway remolding via MAPK/Erk signaling pathway in a dose-dependent manner while the expression of TGF-β1, VEGF, IL-13, and ET-1 were obviously reduced	[56]
5	Icariin	Foam cell	0.8, 4, and 20 mM, for 12 h;	The expression of CD36 was downregulated while SR-BI was upregulated in LPS-induced foam cell when treated by Icariin, while p38/MAPK pathway may act as key pathway in this process.	[58]

i.g.: Oral administration; ROS: reactive oxygen species; Keap: Kelch-like ECH-associated protein; Nrf: NF-E2-related factor; TGF-β: Transforming growth factor-β; MAPK: Mitogen-activated protein kinase; Cadherin: Ca2+dependent cell adhesion molecule; α-SMA: Alpha Sarcomeric Actin; ASMCs: Airway smooth muscle cells; OVA: Ovalbumin; Erk: Extracellular regulated protein kinases; VEGF: Vascular endothelial growth factor; IL: Interleukin; ET: Endothelin; SR-BI: Scavenger receptor class B type I; LPS: Lipopolysaccharide.

Icariin could inhibit airway smooth muscle (ASMC) proliferation

Hyperplasia of airway smooth muscle cells is one of the main manifestations of airway remodeling. The excessive proliferation of ASMC not only promotes the occurrence of airway hyperresponsiveness but also can modify the extracellular matrix and promote the production of inflammatory factors to further aggravate airway inflammation, which seriously affects the prognosis of asthma patients.[54] In vitro experiments have shown that icariin can not only induce S phase acceleration and G2/M phase arrest of airway smooth muscle cells to inhibit cell proliferation but also promote the expression of apoptosis-related genes to promote cell apoptosis.[55] In addition, a study using ovalbumin (OVA)-induced asthmatic mice conducted by Lingli Hu et al. demonstrated that icariin intervention can significantly downregulate the expression of TGF-β1, vascular endothelial growth factor (VEGF), IL-13 (interleukin-13), endothelin-1 (ET-1), and other important cytokines in airway remodeling, inhibiting the activity of the MAPK/Erk signaling pathway and thereby inhibiting the proliferation of AMSCs and improving the airway remodeling process by affecting multiple targets.[56]

Icariin could inhibit the proinflammatory effect of macrophages

Studies have shown that macrophages can not only secrete macrophage migration inhibitory factor (MIF) to promote the secretion of inflammatory factors, but also induce autophagy of ASMC and further induce airway remodeling.[57] In lipopolysaccharide (LPS)-activated macrophages, icariin was found to target the expression of p38MAPK-related signaling factors and inhibit the proinflammatory effect of macrophages.[58] Further studies have shown that macrophages can be further transformed into different phenotypes under the stimulation of different factors. Among them, interferon or lipopolysaccharide (LPS) can induce M1 polarization of macrophages and increase the expression of Th1 proinflammatory factors and corresponding chemokines in the tissue microenvironment; IL-4 or IL-13 can activate the M2 type conversion of macrophages, increasing the expression of anti-inflammatory factors, and promoting tissue repair and anti-inflammatory effects.[59]

Future perspectives

In a randomized placebo-controlled trial with 30 healthy men as subjects, the main active metabolites of icariin in the human body were found to be desmethylicariin and its precursor, which have good tolerance and almost no adverse reactions, providing favorable evidence for further investment in clinical treatment.[60] In addition, in a randomized controlled trial of 100 postmenopausal women, icariin was found to significantly inhibit bone resorption, stimulate bone formation, and effectively delay the occurrence of postmenopausal osteoporosis.[61] At present, the traditional Chinese medicine prescription "ChuanKeZhi Injection" with icariin as one of the main components has been widely used in the treatment of clinical respiratory diseases. It has shown many benefits such as antiallergic and anti-inflammatory effects and enhancement of body fluid and cellular immunity.[62] This evidence vouches for the high safety of the clinical application of icariin and its feasibility in treating asthma, providing support for further clinical application of icariin. Due to the extensive mechanism of action of icariin, the specific therapeutic mechanism of icariin in the asthmatic population remains to be further clarified.

Conclusion

The pathogenesis of asthma is complicated, and airway inflammation and airway remodeling are the main features of asthma. The use of Epimedium to treat asthma has been proposed in various Chinese medicine prescriptions. Icariin is an effective extract of Epimedium. With its high safety and effective anti-inflammatory, antioxidant, and immune regulation effects, extensive attention has been given to its clinical applications. Icariin can not only effectively inhibit airway inflammation and regulate various immune imbalances in asthma but also effectively improve airway fibrosis and collagen deposition in the airway wall, and reverse the airway remodeling process. In addition, icariin can also cooperate with glucocorticoids to effectively improve the occurrence of hormone resistance and enhance the effect of hormone therapy. More noteworthy is that as a new type of drug carrier, exosomes are being studied extensively. The delivery of icariin through exosomes may effectively enhance drug activity and bioavailability, which can be a promising treatment in future clinical research. Icariin is an effective treatment for asthma, and its specific mechanism and further clinical applications need to be explored continuously.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and publication of this article.

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References

1. Tyler SR, Bunyavanich S. Leveraging-omics for asthma endotyping. J Allergy Clin Immunol. 2019 Jul;144(1):13–23. https://doi.org/10.1016/j.jaci.2019.05.015

2. Prabhala P, Wright DB, Robbe P, Bitter C, Pera T, Ten Hacken NHT, et al. Laminin α4 contributes to airway remodeling and inflammation in asthma. Am J Physiol Lung Cell Mol Physiol. 2019 Dec 1;317(6):L768–L777. https://doi.org/10.1152/ajplung.00222.2019
3. Stokes JR, Casale TB. Characterization of asthma endotypes: implications for therapy. Ann Allergy Asthma Immunol. 2016 Aug;117(2):121–125. https://doi.org/10.1016/j.anai.2016.05.016
4. Casale TB. Biologics and biomarkers for asthma, urticaria, and nasal polyposis. J Allergy Clin Immunol. 2017 May;139(5):1411–1421. https://doi.org/10.1016/j.jaci.2017.03.006
5. Ramakrishnan RK, Al Heialy S, Hamid Q. Role of IL-17 in asthma pathogenesis and its implications for the clinic. Expert Rev Respir Med. 2019 Nov;13(11):1057–1068. https://doi.org/10.1080/17476348.2019.1666002
6. Wang AL, Panganiban R, Qiu W, Kho AT, Chupp G, Meyers DA, et al. Drug repurposing to treat glucocorticoid resistance in asthma. J Pers Med. 2021 Mar 3;11(3):175. https://doi.org/10.3390/jpm11030175
7. Wang Y, Chen YJ, Xiang C, Jiang GW, Xu YD, Yin LM, et al. Discovery of potential asthma targets based on the clinical efficacy of traditional Chinese medicine formulas. J Ethnopharmacol. 2020 Apr 24; 252:112635. https://doi.org/10.1016/j.jep.2020.112635
8. Ma H, He X, Yang Y, Li M, Hao D, Jia Z. The genus Epimedium: an ethnopharmacological and phytochemical review. J Ethnopharmacol. 2011 Apr 12;134(3):519–541. https://doi.org/10.1016/j.jep.2011.01.001
9. Chen M, Wu J, Luo Q, Mo S, Lyu Y, Wei Y, et al. The anticancer properties of Herba Epimedii and its main bioactive Componentsicariin and Icariside II. Nutrients. 2016 Sep 13;8(9):563. https://doi.org/10.3390/nu8090563
10. Zhao JF, Xu JY, Xu YE, Chen SL, Guo YX, Gao QY, et al. High-throughput metabolomics method for discovering metabolic biomarkers and pathways to reveal effects and molecular mechanism of ethanol extract from *Epimedium* against osteoporosis. Front Pharmacol. 2020 Aug 27;11:1318. https://doi.org/10.3389/fphar.2020.01318
11. Huang W, Song Y, Wang L. Wenshen decoction suppresses inflammation in IL-33-induced asthma murine model via inhibiting ILC2 activation. Ann Transl Med. 2019 Oct;7(20):570. https://doi.org/10.21037/atm.2019.09.34
12. Kim JY, Shim SH. *Epimedium koreanum* extract and its flavonoids reduced atherosclerotic risk via suppressing modification of human HDL. Nutrients. 2019 May 18;11(5):1110. https://doi.org/10.3390/nu11051110
13. Jiang J, Jie S, Jia XB. Phytochemistry and ethnopharmacology of Epimedium L. species. Chinese Herbal Med. 2015;7(3):204–222. https://doi.org/10.1016/S1674-6384(15)60043-0
14. Cao LH, Qiao JY, Huang HY, Fang XY, Zhang R, Miao MS, et al. PI3K-AKT signaling activation and icariin: the potential effects on the perimenopausal depression-like rat model. Molecules. 2019 Oct 15;24(20):3700. https://doi.org/10.3390/molecules24203700
15. Chen S, Wang Z, Zhou H, He B, Hu D, Jiang H. Icariin reduces high glucose-induced endothelial progenitor cell dysfunction via inhibiting the p38/CREB pathway and activating the Akt/eNOS/NO pathway. Exp Ther Med. 2019 Dec;18(6):4774–4780. https://doi.org/10.3892/etm.2019.8132
16. Wang M, Gao H, Li W, Wu B. Icariin and its metabolites regulate lipid metabolism: from effects to molecular mechanisms. Biomed Pharmacother. 2020 Nov; 131:110675. https://doi.org/10.1016/j.biopha.2020.110675
17. Xiao H, Wignall N, Brown ES. An open-label pilot study of icariin for co-morbid bipolar and alcohol use disorder. Am J Drug Alcohol Abuse. 2016;42(2):162–167. https://doi.org/10.3109/00952990.2015.1114118
18. Wu X, Kong W, Qi X, Wang S, Chen Y, Zhao Z, et al. Icariin induces apoptosis of human lung adenocarcinoma cells by activating the mitochondrial apoptotic pathway. Life Sci. 2019 Dec 15; 239:116879. https://doi.org/10.1016/j.lfs.2019.116879
19. Qi C, Shao Y, Liu X, Wang D, Li X. The cardioprotective effects of icariin on the isoprenaline-induced takotsubo-like rat model: involvement of reactive oxygen species and the TLR4/NF-κB signaling pathway. Int Immunopharmacol. 2019 Sep;74:105733. https://doi.org/10.1016/j.intimp.2019.105733
20. Xie Y, Sun W, Yan F, Liu H, Deng Z, Cai L. Icariin-loaded porous scaffolds for bone regeneration through the regulation of the coupling process of osteogenesis and osteoclastic activity. Int J Nanomedicine. 2019 Aug 1;14:6019–6033. https://doi.org/10.2147/IJN.S203859
21. Matucci A, Vultaggio A, Maggi E, Kasujee I. Is IgE or eosinophils the key player in allergic asthma pathogenesis? Are we asking the right question? Respir Res. 2018 Jun 8;19(1):113. https://doi.org/10.1186/s12931-018-0813-0
22. Pal K, Feng X, Steinke JW, Burdick MD, Shim YM, Sung SS, et al. Leukotriene A4 hydrolase activation and leukotriene B4 production by eosinophils in severe asthma. Am J Respir Cell Mol Biol. 2019 Apr;60(4):413–419. https://doi.org/10.1165/rcmb.2018-0175OC
23. Kabashima K, Nakashima C, Nonomura Y, Otsuka A, Cardamone C, Parente R, et al. Biomarkers for evaluation of mast cell and basophil activation. Immunol Rev. 2018 Mar;282(1):114–120. https://doi.org/10.1111/imr.12639
24. Wang J, Wu J, Kong L, Nurahmat M, Chen M, Luo Q, et al. BuShenYiQi formula strengthens Th1 response and suppresses Th2-Th17 responses in RSV-induced asthma exacerbated mice. J Ethnopharmacol. 2014 May 28;154(1):131–147. https://doi.org/10.1016/j.jep.2014.03.041
25. Wei Y, Luo QL, Sun J, Chen MX, Liu F, Dong JC. Bu-Shen-Yi-Qi formulae suppress chronic airway inflammation and regulate Th17/Treg imbalance in the murine ovalbumin asthma model. J Ethnopharmacol. 2015 Apr 22;164:368–377. https://doi.org/10.1016/j.jep.2015.01.016
26. Du WJ, Dong JC, Cai C. [Effects of icariin on Bcl-2 and Bax protein expressions and eosinophils apoptosis in bronchial asthmatic mice]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2011 Sep;31(9):1248–1253. Chinese.
27. Bošnjak B, Kazemi S, Altenburger LM, Mokrović G, Epstein MM. Th2-T RMs maintain life-long allergic memory in experimental asthma in mice. Front Immunol. 2019 Apr 24;10:840. https://doi.org/10.3389/fimmu.2019.00840
28. Holgate ST. Innate and adaptive immune responses in asthma. Nat Med. 2012 May 4;18(5):673–683. https://doi.org/10.1038/nm.2731
29. Pang L, Yu P, Liu X, Fan Y, Shi Y, Zou S. Fine particulate matter induces airway inflammation by disturbing the balance between Th1/Th2 and regulation of GATA3 and Runx3 expression in BALB/c mice. Mol Med Rep. 2021 May;23(5):378. https://doi.org/10.3892/mmr.2021.12017
30. Rhew KY, Han Y. Immunoadjuvant activity of icariin that induces Th1-type antibody in mice. Arch Pharm Res. 2012 Sep;35(9):1685–1691. https://doi.org/10.1007/s12272-012-0920-2
31. Xu CQ, LE JJ, Duan XH, DU WJ, Liu BJ, Wu JF, et al. Molecular mechanism of icariin on rat asthmatic model. Chin Med J (Engl). 2011 Sep;124(18):2899–2906.
32. Chen Q, Guo X, Deng N, Liu L, Chen S, Wang A, et al. α-Galactosylceramide treatment before allergen sensitization promotes iNKT cell-mediated induction of Treg cells, preventing Th2 cell responses in murine asthma. J Biol Chem. 2019 Apr 5;294(14):5438–5455. https://doi.org/10.1074/jbc.RA118.005418
33. Jing W, Wang W, Liu Q. Passive smoking induces pediatric asthma by affecting the balance of Treg/Th17 cells.

Pediatr Res. 2019 Mar;85(4):469–476. https://doi.org/10.1038/s41390-019-0276-0
34. Wei Y, Liu B, Sun J, Lv Y, Luo Q, Liu F, et al. Regulation of Th17/Treg function contributes to the attenuation of chronic airway inflammation by icariin in ovalbumin-induced murine asthma model. Immunobiology. 2015 Jun;220(6):789–797. https://doi.org/10.1016/j.imbio.2014.12.015
35. Bing J, Li YY, Yang WJ, Zhang LZ, Fang M S, Fu HY, et al. Jinkui Shenqi pills ameliorate asthma with "kidney yang deficiency" by enhancing the function of the hypothalamic-pituitary-adrenal axis to regulate T helper 1/2 imbalance. Evid Based Complement Alternat Med. 2018 Feb 8;2018:7253240. https://doi.org/10.1155/2018/7253240
36. Kim SH, Kim DH, Lavender P, Seo JH, Kim YS, Park JS, et al. Repression of TNF-alpha-induced IL-8 expression by the glucocorticoid receptor-beta involves inhibition of histone H4 acetylation. Exp Mol Med. 2009 May 31;41(5):297–306. https://doi.org/10.3858/emm.2009.41.5.033
37. He Y, Shi J, Nguyen QT, You E, Liu H, Ren X, et al. Development of highly potent glucocorticoids for steroid-resistant severe asthma. Proc Natl Acad Sci U S A. 2019 Apr 2;116(14):6932–6937. https://doi.org/10.1073/pnas.1816734116
38. Kong L, Liang X, Liu A, Yang X, Luo Q, Lv Y, et al. Icariin inhibits inflammation via immunomodulation of the cutaneous hypothalamus-pituitary-adrenal axis in vitro. Clin Exp Dermatol. 2019 Mar;44(2):144–152. https://doi.org/10.1111/ced.13735
39. Sun X, Deng X, Cai W, Li W, Shen Z, Jiang T, et al. Icariin inhibits LPS-induced cell inflammatory response by promoting GRα nuclear translocation and upregulating GRα expression. Life Sci. 2018 Feb 15;195:33–43. https://doi.org/10.1016/j.lfs.2018.01.006
40. Tang X, Nian H, Li X, Yang Y, Wang X, Xu L, et al. Effects of the combined extracts of Herba Epimedii and Fructus Ligustrilucidi on airway remodeling in the asthmatic rats with the treatment of budesonide. BMC Complement Altern Med. 2017 Aug 1;17(1):380. https://doi.org/10.1186/s12906-017-1891-0
41. Uchida Y, Soma T, Nakagome K, Kobayashi T, Nagata M. Implications of prostaglandin D2 and leukotrienes in exhaled breath condensates of asthma. Ann Allergy Asthma Immunol. 2019 Jul;123(1):81–88.e1. https://doi.org/10.1016/j.anai.2019.04.008
42. Johnsson AK, Choi JH, Rönnberg E, Fuchs D, Kolmert J, Hamberg M, et al. Selective inhibition of prostaglandin D biosynthesis in human mast cells to overcome need for multiple receptor antagonists: biochemical consequences. Clin Exp Allergy. 2021 Apr;51(4):594–603. https://doi.org/10.1111/cea.13831
43. Qiao J, Sun S, Yuan L, Wang J. Effects of icariin on asthma mouse model are associated with regulation of prostaglandin D2 level. Allergol Immunopathol (Madr). 2017 Nov-Dec;45(6):567–572. https://doi.org/10.1016/j.aller.2017.02.007
44. Qin W, Wu X, Jia Y, Tong X, Guo C, Chen D, et al. Suhuang antitussive capsule inhibits NLRP3 inflammasome activation and ameliorates pulmonary dysfunction via suppression of endoplasmic reticulum stress in cough variant asthma. Biomed Pharmacother. 2019 Oct;118:109188. https://doi.org/10.1016/j.biopha.2019.109188
45. Kim HK, Lee GH, Bhattarai KR, Junjappa RP, Lee HY, Handigund M, et al. PI3Kδ contributes to ER stress-associated asthma through ER-redox disturbances: the involvement of the RIDD-RIG-I-NF-κB axis. Exp Mol Med. 2018 Feb 16;50(2):e444. https://doi.org/10.1038/emm.2017.270
46. Liu J, Liu L, Sun J, Luo Q, Yan C, Zhang H, et al. Icariin protects hippocampal neurons from endoplasmic reticulum stress and NF-κB mediated apoptosis in fetal rat hippocampal neurons and asthma rats. Front Pharmacol. 2020 Jan 31;10:1660. https://doi.org/10.3389/fphar.2019.01660
47. Vieira CP, de Oliveira LP, Da Silva MB, Majolli Andre D, Tavares EBG, Pimentel ER, et al. Role of metalloproteinases and TNF-α in obesity-associated asthma in mice. Life Sci. 2020 Oct 15;259:118191. https://doi.org/10.1016/j.lfs.2020.118191
48. Yao Z, Fu Y. Glycyrrhizic acid restrains airway inflammation and remodeling in asthma via the TGF-β1/Smad signaling pathway. Exp Ther Med. 2021 May;21(5):461. https://doi.org/10.3892/etm.2021.9892
49. Wang K, Zheng X, Pan Z, Yao W, Gao X, Wang X, et al. Icariin prevents extracellular matrix accumulation and ameliorates experimental diabetic kidney disease by inhibiting oxidative stress via GPER mediated p62-dependent Keap1 degradation and Nrf2 activation. Front Cell Dev Biol. 2020 Jul 17;8:559. https://doi.org/10.3389/fcell.2020.00559
50. Song Y, Wang Z, Jiang J, Piao Y, Li L, Xu C, et al. DEK-targeting aptamer DTA-64 attenuates bronchial EMT-mediated airway remodeling by suppressing TGF-β1/Smad, MAPK and PI3K signaling pathway in asthma. J Cell Mol Med. 2020 Dec;24(23):13739–13750. https://doi.org/10.1111/jcmm.15942
51. Sun Z, Ji N, Ma Q, Zhu R, Chen Z, Wang Z, et al. Epithelial-mesenchymal transition in asthma airway remodeling is regulated by the IL-33/CD146 axis. Front Immunol. 2020 Jul 22;11:1598. https://doi.org/10.3389/fimmu.2020.01598
52. Fan Q, Jian Y. MiR-203a-3p regulates TGF-β1-induced epithelial-mesenchymal transition (EMT) in asthma by regulating Smad3 pathway through SIX1. Biosci Rep. 2020 Feb 28;40(2):BSR20192645. https://doi.org/10.1042/BSR20192645
53. Li Z, Yuan X, Wang B, Gao F. Icariin alleviates transforming growth factor-β1-induced epithelial-mesenchymal transition by targeting Smad and MAPK signaling pathways. Am J Transl Res. 2020 Feb 15;12(2):343–360. eCollection 2020.
54. Dilasser F, Rose L, Hassoun D, Klein M, Rousselle M, Brosseau C, et al. Essential role of smooth muscle Rac1 in severe asthma-associated airway remodeling. Thorax. 2021 Feb 4;76(4):326–334. https://doi.org/10.1136/thoraxjnl-2020-216271
55. Yang L, Xiao B, Hou L, Zhou G, Mo B, Yao D. Bioactive molecule Icariin inhibited proliferation while enhanced apoptosis and autophagy of rat airway smooth muscle cells in vitro. Cytotechnology. 2019 Dec;71(6):1109–1120. https://doi.org/10.1007/s10616-019-00348-9
56. Hu L, Li L, Zhang H, Li Q, Jiang S, Qiu J, et al. Inhibition of airway remodeling and inflammatory response by Icariin in asthma. BMC Complement Altern Med. 2019 Nov 19;19(1):316. https://doi.org/10.1186/s12906-019-2743-x
57. Li R, Wang F, Wei J, Lin Y, Tang G, Rao L, et al. The role of macrophage migration inhibitory factor (MIF) in asthmatic airway remodeling. Allergy Asthma Immunol Res. 2021 Jan;13(1):88–105. https://doi.org/10.4168/aair.2021.13.1.88
58. Yang H, Yan L, Qian P, Duan H, Wu J, Li B, et al. Icariin inhibits foam cell formation by down-regulating the expression of CD36 and up-regulating the expression of SR-BI. J Cell Biochem. 2015 Apr;116(4):580–588. https://doi.org/10.1002/jcb.25009
59. Saradna A, Do DC, Kumar S, Fu QL, Gao P. Macrophage polarization and allergic asthma. Transl Res. 2018 Jan;191:1–14. https://doi.org/10.1016/j.trsl.2017.09.002
60. Teo YL, Cheong WF, Cazenave-Gassiot A, Ji S, Logan S, Lee ZXK, et al. Pharmacokinetics of prenylflavonoids following oral ingestion of standardized epimedium extract in humans. Planta Med. 2019 Mar;85(4):347–355. https://doi.org/10.1055/a-0806-7673
61. Zhang G, Qin L, Shi Y. Epimedium-derived phytoestrogen flavonoids exert beneficial effect on preventing bone loss in late postmenopausal women: a 24-month randomized, double-blind and placebo-controlled trial. J Bone Miner Res. 2007 Jul;22(7):1072–1079. https://doi.org/10.1359/jbmr.070405
62. Li M, Zheng W, Zhang C, Yan Q, Peng Z, Xie F, et al. Chuankezhi injection for asthma: protocol of a systematic review and meta-analysis. Medicine (Baltimore). 2019 Aug;98(33):e16630. https://doi.org/10.1097/MD.0000000000016630