Systematic Review on Future Therapeutic Targeting SIRT-1, NRF2, HO-1 Pathway with Natural and Synthetic Molecules in Management of Asthma

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DOI: https://doi.org/10.51244/IJRSI.2026.1307000253

Received: 24 July 2026; Accepted: 30 July 2026; Published: 10 August 2026

ABSTRACT

Asthma is a persistent inflammatory respiratory condition that entails airway hyperreactivity, hypersecretion of mucus, obstructed airflow, and airway remodeling. One of the mechanisms of asthma development is oxidative stress, since the excessive production of ROS (reactive oxygen species) leads to exacerbation of inflammation and structural damage to airway epithelium. Currently, one of the most promising therapeutic targets is the SIRT1/NRF2/HO-1 signaling pathway, which is responsible for the regulation of oxidative stress and inflammation. The present systematic review discusses the opportunities for treatment of asthma associated with the modulation of the SIRT1/NRF2/HO-1 signaling pathway. Bioactive natural substances such as resveratrol, curcumin, quercetin, sulforaphane, berberine, and carnosic acid show substantial antioxidant, anti-inflammatory, and cytoprotective activities by upregulation of SIRT1 and NRF2 pathways resulting in induction of HO-1 and prevention of oxidative stress. Unfortunately, their clinical use is hindered by low bioavailability and instability due to rapid metabolism and unfavorable pharmacokinetics. Synthetic agents like SRT1720, SRT2104, dimethyl fumarate (DMF), bardoxolone methyl, and others as NRF2 agonists provide higher stability and efficacy in comparison with natural counterparts and can be considered as promising candidates for further translational studies and clinical application. Future directions include nanotechnologies for targeted drug delivery and combinatorial therapy. While several preclinical studies have yielded positive outcomes, clinical translation has been hindered by variations in experimental methods, disparities in dosage regimes, and a lack of well-conducted human clinical trials. In summary, modulation of the SIRT1/NRF2/HO-1 signaling pathway is an innovative and attractive approach towards achieving a disease-modifying treatment for asthma. Clinical research is required to determine the safety and efficacy of natural and artificial molecules in the modulation of this pathway in asthma therapy.

Keywords: Asthma, SIRT1, NRF2, HO-1, Oxidative Stress, Natural and Synthetic Molecules

INTRODUCTION

Asthma is a highly prevalent chronic respiratory disease marked by variable airflow obstruction, airway hyper responsiveness, and persistent inflammation. Despite existing therapies, many patients especially those with severe or steroid-resistant asthma continue to experience symptoms and progressive airway remodeling. This underscores the need for novel therapeutic strategies that target underlying molecular dysfunctions beyond conventional anti-inflammatory approaches [1]. One promising target is the SIRT1 pathway. SIRT1, a NAD^+ dependent deacetylase, regulates inflammation, oxidative stress, and cellular stress responses [2,3,4]. In asthma, SIRT1 expression is dysregulated; reduced SIRT1 activity is linked to enhanced cytokine production and airway inflammation. Experimental activation of SIRT1 using the synthetic molecule SRT1720 suppresses inflammatory-cell infiltration and Th2 cytokine release in OVA-induced asthma mouse models Moreover, natural activators like resveratrol also act via SIRT1 to inhibit pro-inflammatory signaling in immune cells, further supporting SIRT1's therapeutic relevance [5,6].

Oxidative stress is another central feature of asthma pathogenesis. The transcription factor NRF2 orchestrates antioxidant defenses via downstream genes like HO-1 [7,8,9]. In murine models, genetic activation of NRF2 specifically in airway epithelial (club) cells reduces allergen-induced airway hyperresponsiveness, Th2

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue VII July 2026

inflammation, and mucus production, and improves epithelial barrier integrity via upregulation of tightjunction proteins (while loss of NRF2 worsens allergen-induced asthma) together highlighting its protective role [10,11,12]. Importantly, in models of neutrophilic (IL-17–driven) asthma, NRF2 deficiency aggravates inflammation, suggesting that NRF2 may modulate not only classical eosinophilic asthma but also more severe, steroid-resistant phenotypes [13,14].

Given the interconnected roles of SIRT1, NRF2, and HO-1 in regulating inflammation and redox balance, targeting this axis presents a compelling therapeutic strategy. For example, dimethyl fumarate (DMF), a known NRF2 activator, was recently shown to alleviate allergic asthma in mice by boosting NRF2 signaling in regulatory T cells, thereby reducing Th2 and Th17 cytokine production and improving disease outcomes (preclinical data need formal citation). Furthermore, bergenin, a natural SIRT1 agonist, ameliorates airway inflammation and remodeling in a macrophage-dependent asthma model via SIRT1–NF-κB modulation [6, 8].

Together, these studies point to a therapeutic axis SIRT1 → NRF2 → HO-1 that could be leveraged by both natural and synthetic molecules to provide additive or synergistic benefits in asthma. However, despite strong preclinical evidence, translation to clinical use remains limited underscoring the need for a systematic review to critically evaluate and compare preclinical and early clinical data for SIRT1/NRF2/HO-1 modulators, identify the most promising candidate molecules, and highlight gaps for future research.

Pathophysiology of Asthma

Asthma is a heterogeneous airway disease driven by chronic airway inflammation, variable airflow obstruction, and airway hyperresponsiveness (AHR) producing episodic wheeze, dyspnea, and cough. Multiple immune endotypes underlie asthma: classical Type-2 (Th2/eosinophilic) inflammation mediated by IL-4, IL-5 and IL13; non-Type-2 phenotypes including Th17/neutrophilic inflammation; and mixed or pauci-inflammatory forms explaining variable treatment responses. A central and convergent driver across endotypes is oxidative stress: increased production of reactive oxygen and nitrogen species (ROS/RNS) from inflammatory cells, epithelial cells and mitochondria together with impaired antioxidant defenses amplifies inflammation and injures the airway wall [15, 16, 17]. Sources of ROS in the asthmatic airway include NADPH oxidases, mitochondrial dysfunction, and activated inflammatory cells (eosinophils, neutrophils, macrophages); these ROS promote redox-sensitive signaling that increases cytokine release, mucus production and AHR [18]. Oxidative stress also impairs the function of structural cells airway epithelial cells and airway smooth muscle (ASM) weakening barrier integrity, increasing mucus metaplasia, and enhancing ASM contractility and proliferation; these contribute to persistent airflow limitation and remodeling. In severe or steroid-resistant asthma, neutrophilic and IL-17 driven pathways often prevail; these phenotypes are particularly associated with oxidative stress signatures and reduced corticosteroid responsiveness [15,16,18]. Airway remodeling a combination of subepithelial fibrosis, increased smooth muscle mass, angiogenesis and goblet-cell hyperplasia arises from chronic inflammatory and oxidative signaling, and diminishes reversibility of obstruction, driving long-term morbidity [19,20].

Pathway Overview: SIRT-1, NRF2, HO-1 Pathway Overview

SIRT-1

- SIRT-1 is part of the sirtuin family of NAD^+-dependent deacetylases involved in transcription, metabolism, DNA repair, apoptosis, and stress responses.
- Functions as an NAD^+-dependent lysine deacylase, removing acetyl groups from histones and proteins like NF-κB
- This deacetylation suppresses pro-inflammatory gene expression and supports cell survival during stress. [21,22]
- In the lungs, SIRT-1 helps by:Reducing cytokine production Limiting inflammatory-cell recruitment and Enhancing antioxidant defenses

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue VII July 2026

- SIRT-1 is active in airway epithelial cells and immune cells.
- Modulating SIRT-1 (via natural or synthetic activators) reduces airway inflammation and improves features of experimental asthma [23,24,25].

NRF2

- NRF2 is a transcription factor normally bound by its inhibitor KEAP1, leading to its degradation under nonstress conditions [26–29]. During oxidative/electrophilic stress:
  - KEAP1 cysteine residues get modified
  - KEAP1–NRF2 interaction is disrupted.
  - NRF2 stabilizes and enters the nucleus.

In the nucleus, NRF2 binds AREs (antioxidant response elements) with small Maf proteins [30].

NRF2 activation induces antioxidant and cytoprotective genes such as:

- HO-1
- NQO1
- GCLC

These responses help to: Restore redox balance

- Reduce lipid peroxidation
- Lower airway inflammation [31,32,33].

HO-1

- HO-1 is a major NRF2-regulated gene and a cytoprotective enzyme [34, 35].
- Converts heme into:
  - Biliverdin
- Carbon monoxide (CO)
- Ferrous iron
- These products exert:
- Antioxidant effects
- Anti-apoptotic effects
- Anti-inflammatory actions
- In airway cells, HO-1 helps by:
- Reducing epithelial injury

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue VII July 2026

- Limiting inflammatory signaling
- Suppressing certain types of regulated cell death that worsen inflammation
- Activation of the KEAP1–NRF2–ARE pathway is the main way to increase HO-1 expression and obtain its protective benefits in respiratory diseases [36, 37].

Interlinkage of SIRT-1 — NRF2 — HO-1

Functionally, SIRT-1 can enhance NRF2-dependent antioxidant responses (directly or indirectly stabilizing NRF2 activity and modifying upstream regulators), forming a positive feedback loop that amplifies ARE driven gene expression including HO-1. This SIRT1 ↔ NRF2 ↔ HO-1 interplay provides an integrated anti-inflammatory and antioxidative program: activating SIRT-1 both suppresses pro-inflammatory transcription (e.g., via deacetylation of NF-κB) and potentiates NRF2-mediated antioxidant gene expression, together protecting airway epithelial and immune cells from oxidative injury and reducing the hallmarks of asthma in preclinical models [38, 39,40].

Role of SIRT-1, NRF2, HO-1 in Asthma

The SIRT-1 / NRF2 / HO-1 axis acts as a major cellular defense pathway in asthma, counteracting oxidative stress, inflammatory cytokine production, airway remodeling, and epithelial injury. SIRT-1, a NAD^+-dependent deacetylase, functions as an upstream regulator that suppresses pro-inflammatory signaling and improves antioxidant capacity [22, 25, 23]. Multiple asthma models demonstrate that restoring SIRT-1 expression reduces Th2 cytokines (IL-4, IL-5, IL-13), decreases lipid peroxidation, and lowers ROS accumulation, as observed with quercetin and pterostilbene treatment [42, 44, 43]. SIRT-1 also modifies the activity of transcription factors such as NRF2 by regulating its acetylation status; reduced NRF2 acetylation enhances its nuclear stability and promotes antioxidant gene transcription a mechanism supported in cell studies [38]. Once activated, NRF2 translocate into the nucleus and binds AREs, stimulating the production of antioxidant enzymes including HO-1, NQO1, and GCLC [27, 31, 30]. Activation of NRF2 in asthma models treated with pterostilbene (and other NRF2-inducers) was associated with decreased airway inflammation, reduced oxidative stress markers, improved airway hyper responsiveness, and protection against epithelial damage [43, 32]. HO-1, a central downstream effector of NRF2, plays a central role in degrading heme into biliverdin, carbon monoxide, and iron molecules known for their anti-inflammatory, anti-apoptotic, and antioxidant activity [33, 34, 35] HO-1 induction has been shown to suppress airway remodeling, reduce epithelial cell apoptosis, and restore redox balance in inflamed lungs tissue. [33, 34, 36] Collectively, the coordinated activation of SIRT-1 → NRF2 → HO-1 creates a synergistic protective network in asthma. SIRT-1 activation initiates anti-inflammatory and antioxidant effects; NRF2 amplifies cellular defense through ARE-mediated transcription; and HO-1 executes cytoprotective functions. The combined action of this triad reduces airway inflammation, prevents structural remodeling, counters oxidative injury, and significantly alleviates asthma pathology in vivo. This makes the SIRT-1 / NRF2 / HO-1 axis an attractive therapeutic target for both natural compounds (quercetin, zingerone, bergenin) and novel synthetic drugs.

Natural Compounds Targeting SIRT-1/NRF2/HO-1

Natural Compound	Mechanism of Action	Pathway Activated (SIRT1 / NRF2 / HO-1)	Effects in Airway & Asthma Models
Resveratrol [13,45,46]	Activates SIRT1 (NAD^+-dependent deacetylase); enhances Nrf2 signaling by modulating Keap1regulated stabilization; increases nuclear Nrf2 and ARE gene transcription.	SIRT1 → Nrf2 → HO-1	Reduces oxidative markers, airway inflammation, and improves antioxidant defense in rodent airway/obesity-asthma models; supports role as upstream SIRT1/Nrf2 activator.

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Curcumin [55,56]	Disrupts Keap1–Nrf2 interaction (electrophilic action); stabilizes and activates Nrf2; induces HO-1; additionally inhibits NF-κB contributing to anti-inflammatory action.	Nrf2 → HO-1 (primary) and NF-κB inhibition	Increases Nrf2/HO-1, reduces cytokines and oxidative damage, improves lung function and attenuates inflammation in multiple rodent airway injury models.
Quercetin [42,44]	Upregulates SIRT1 and Nrf2; increases HO-1; inhibits ferroptosis, decreases ROS and lipid peroxidation.	SIRT1 → Nrf2 → HO-1	In OVA-asthma models, restores SIRT1/Nrf2/HO-1 expression, decreases Th2 cytokines, reduces oxidative stress, and alleviates airway inflammation & hyperresponsiveness.
Sulforaphane [60]	Covalently modifies Keap1 cysteines, stabilizing NRF2; enhances nuclear translocation and ARE activation leading to HO-1 induction.	Nrf2 → HO-1	In mice and human pilot studies increases NRF2 enzymes in airway epithelium; improves antioxidant responses, reduces oxidative damage, and shows bronchoprotective effects (though mixed clinical translation).
Carnosic Acid	Activates Nrf2/ARE signaling; upregulates Nrf2 & HO-1; inhibits NF-κB and MAPK pathways; reduces ROS production.	Nrf2 → HO-1 + antiinflammatory (NFκB inhibition)	Shows strong antioxidant and anti-inflammatory effects in preclinical lung models; reduces ROS, inflammatory mediators, and improves cell survival, supporting role as Nrf2-based therapy.

Synthetic Molecule Targeting SIRT-1/NRF2/HO-1

Compound	Mechanism of Action (MOA)	Pathway Activation	Effects in Asthma Models
SRT1720 [2,4,5,9]	• High-affinity SIRT1 activator		
	• Increases NF-κB p65 deacetylation → lowers inflammation • Activates FoxO3a → ↑ antioxidant genes	• SIRT1 ↑ (primary) • NRF2 ↑ (indirect via ROS reduction)	• ↓ IL-4, IL-5, IL-13 • ↓ Eosinophils • ↓ MUC5AC (mucus)
	• Stabilizes mitochondria → ↓ ROS		• ↓ AHR
		• HO-1 ↑	• ↑ SOD, HO-1
Dimethyl Fumarate (DMF) [27,29]	• Alkylates Keap1 → stabilizes NRF2 • ↑ Glutathione synthesis	• NRF2 ↑ • HO-1 ↑ • No direct	• ↓ AHR • ↓ IL-1β, IL-6, TNF-α • ↓ Eosinophils &

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue VII July 2026

	• Suppresses NF-κB via ROS reduction	SIRT1 effect	neutrophils Restores epithelial barrier • ↑ HO-1 & antioxidant genes
Bardoxolone Methyl (CDDO-Me) [27,29,31]	• Synthetic oleanolic acid derivative • Disrupts Keap1–NRF2 binding • ↓ Mitochondrial ROS • Suppresses STAT6 → ↓ Th2 signaling	• NRF2 ↑↑ • HO-1 ↑ • Minimal SIRT1 effect	• ↓ Th2 cytokines (IL-4, IL-5, IL-13) • ↓ Collagen & remodeling • ↓ Oxidative stress • ↑ GSH • ↓ MUC5AC
Theophylline (Low Dose)	• Activates SIRT1 & HDAC2 • Restores steroid sensitivity	• SIRT1 ↑ • HDAC2 ↑	• ↓ Steroid resistance • ↓
	• PDE inhibition → ↑ cAMP	• Weak NRF2 stabilization	Neutrophilic inflammation ↓ IL-17, TNF-α • ↑ ICS sensitivity ↓ Airway obstruction & AHR
Rosiglitazone (PPAR-γ Agonist) [22,24,25]	• Activates PPAR-γ → ↑ SIRT1 • ↑ Mitochondrial biogenesis • Inhibits NF-κB & STAT6 • Promotes M2 macrophages	• SIRT1 ↑ • Mild NRF2 ↑ • HO-1 ↑	• ↓ Eosinophils & neutrophils • ↓ IL-4, IL-5 • ↓ Fibrosis (collagen deposition) • ↓ MUC5AC mucus • ↑ HO-1, GCLM

models. However, asthma-specific human trials remain lacking. Conversely, synthetic activators such as DMF and bardoxolone methyl (triterpenoids) have been engineered to overcome these limitations, offering more predictable pharmacokinetics, controlled dosing, and durable target engagement. These properties underpin their stronger and more reproducible anti-asthmatic responses seen preclinical.

Future Prospective Therapies

Mesenchymal Stem Cell (MSC) Therapy

Recent studies are exploring innovative therapies that aim not just to control asthma symptoms but to transform how the disease behaves. One promising direction is the use of mesenchymal stem cells (MSCs), which have the ability to calm inflammation, repair damaged airway lining, and restore overall immune

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue VII July 2026

balance. These benefits come from their direct interaction with immune cells as well as the healing molecules they release.

CAR-NK cell therapy

Another exciting approach focuses on CAR-NK cell therapy, a next-generation immune treatment. Unlike traditional CAR-T cells, these engineered natural killer cells can be used more safely and may target harmful asthma-driving cells like eosinophils or IgE-producing B-cells with greater precision. This could help reshape the immune response and reduce long-term airway inflammation. [52-54]

Future Therapeutic Potential & Challenges

The growing interest in redox-modulating therapies for asthma has led to extensive evaluation of both natural and synthetic molecules targeting the SIRT1/NRF2/HO-1 axis, which plays a crucial role in suppressing oxidative stress, airway inflammation, and remodeling. Natural molecules, such as resveratrol, curcumin, quercetin, apigenin, hesperidin, luteolin, sulforaphane, carnosic acid, and berberine, demonstrate strong anti-inflammatory and antioxidant activity largely by activating NRF2 and HO-1, and in some cases enhancing SIRT1-mediated deacetylation of NF-κB, resulting in reduced eosinophilic infiltration and airway hyperresponsiveness (AHR). Antioxidants (Sulforaphane review; Info taken from and I, which reported that sulforaphane induces HO-1 expression and reduces airway inflammation). Similarly, curcumin and quercetin have been repeatedly documented to elevate NRF2 and HO-1 while suppressing Th2 cytokines. However, despite strong efficacy in preclinical asthma models, natural compounds often face major pharmacological limitations including poor solubility, instability, rapid metabolism, and low bioavailability, resulting in insufficient therapeutic levels in lung tissue These challenges have driven interest toward synthetic or semi-synthetic molecules such as SRT1720, SRT2104 (SIRT1 activators), dimethyl fumarate (DMF), bardoxolone methyl (NRF2 activators), TBHQ, and HO-1 inducers like CoPP and hemin, which demonstrate stronger potency and more predictable pharmacokinetics. For example, dimethyl fumarate strongly activates NRF2 and suppresses airway inflammation while SRT1720 reduces airway remodeling through SIRT1 activation (Info from). Synthetic compounds generally show higher efficacy and longer duration of action due to greater stability and targeted activation of signaling pathways. Comparatively, while natural molecules excel in safety and multi-target activity, synthetic agents often show superior potency, better lung distribution, and higher clinical readiness, with agents like DMF and bardoxolone already evaluated in human inflammatory diseases Although natural compounds rarely reach clinical trials for asthma due to bioavailability limitations, their therapeutic potential can be enhance SIRT1-mediated deacetylation of NF-κB, resulting in reduced eosinophilic infiltration and airway hyperresponsiveness (AHR). These effects have been highlighted in studies such as Antioxidants (Sulforaphane review; Info taken from and I, which reported that sulforaphane induces HO-1 expression and reduces airway inflammation). Similarly, curcumin and quercetin have been repeatedly documented to elevate NRF2 and HO-1 while suppressing Th2 cytokines.

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Comparatively, while natural molecules excel in safety and multi-target activity, synthetic agents often show superior potency, better lung distribution, and higher clinical readiness, with agents like DMF and bardoxolone already evaluated in human inflammatory diseases Although natural compounds rarely reach clinical trials for asthma due to bioavailability limitations, their therapeutic potential can be enhance enhanced through nanotechnology-based delivery systems such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles, which increase lung deposition, improve stability, and enhance SIRT1/NRF2/HO-1 activation.

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue VII July 2026

Combination therapies pairing natural polyphenols with synthetic NRF2 or SIRT1 activators are emerging as a promising strategy to achieve synergistic antioxidant responses while reducing drug dosage and toxicity. Despite promising preclinical outcomes, major challenges remain including limited translation to human studies, variability in response, and the need for standardized dosing. All papers agree that more robust clinical trials are urgently required to validate the therapeutic potential of SIRT1/NRF2/HO-1 modulators for asthma, particularly to assess long-term safety, lung-targeted delivery, and comparative efficacy between natural and synthetic molecules. [55,56,57]

Limitations of Current Evidence

Current evidence on therapeutic modulation of the SIRT-1/NRF2/HO-1 axis in asthma remains limited due to several fundamental gaps in preclinical and clinical research. A major limitation is the extensive variability in animal asthma models, including differences in sensitization antigen (OVA vs. house dust mite), species used, and routes of allergen challenge, which creates inconsistent inflammatory phenotypes and reduces comparability across studies These papers clearly explain that OVA-induced models often fail to represent the chronic, mixed-cell inflammation seen in human asthma, thereby restricting translational relevance Additionally, variations in administration routes (intraperitoneal, intranasal, aerosol) and dosing schedules of natural and synthetic compounds further complicate interpretation of therapeutic efficacy.

Another major limitation is the scarcity of human clinical trials evaluating SIRT-1, NRF2, or HO-1– targeting molecules. For example, sulforaphane one of the few NRF2 activators tested in humans showed only modest and inconsistent antioxidant responses, partly due to short intervention duration and variable patient response, highlighting the need for larger, well-controlled trials Furthermore, systematic reviews of complementary and natural asthma therapies report that many clinical studies suffer from small sample sizes, heterogeneous study designs, and lack of standardized formulations, which weakens the strength of current conclusions.

A further barrier is the poor bioavailability of natural molecules such as curcumin, quercetin, and resveratrol, which limits effective activation of the SIRT-1/NRF2/HO-1 pathway in vivo). These molecules undergo rapid metabolism and exhibit low systemic absorption, requiring either high doses or advanced delivery systems, thereby contributing to inconsistent results across studies Collectively, the limitations across animal models, dosing strategies, and human clinical data indicate that while targeting the SIRT-1/NRF2/HO-1 pathway holds strong therapeutic promise, more standardized preclinical protocols and larger human trials are essential before clinical translation can be fully realized [58,59,60]

DISCUSSION

Current research strongly supports that the SIRT1/NRF2/HO-1 pathway plays a key protective role in asthma by reducing oxidative stress, calming airway inflammation, and preventing long-term damage to lung tissues. A wide range of natural and synthetic molecules can activate this pathway, and laboratory studies consistently show benefits such as improved airway responsiveness, reduced inflammatory cytokines, better antioxidant balance, and decreased airway remodeling. Natural compounds are generally safe and act on multiple pathways, but their poor absorption and limited clinical validation remain challenges. On the other hand, synthetic activators like DMF, SRT1720, and bardoxolone methyl offer stronger and more reliable activation, although asthma-specific human trials are still lacking. Research progress is also slowed by differences in animal models, inconsistent dosing strategies, and a shortage of well-designed clinical studies. Even with these limitations, the overall evidence highlights that targeting the SIRT1/NRF2/HO-1 axis either alone or combined with newer approaches such as stem-cell therapies, microbiome-based interventions, or engineered immune cells could pave the way for truly disease-modifying asthma treatments. Moving forward, high-quality clinical trials and standardized research methods will be essential to turn these molecular discoveries into effective, patient-focused therapies.

CONCLUSION

The SIRT1/NRF2/HO-1 pathway is a key protective axis in asthma, reducing oxidative stress, inflammation, and airway remodeling. Both natural and synthetic activators show promising preclinical effects, though

natural compounds face bioavailability challenges, and synthetic agents lack asthma specific clinical trials. Despite variability in models and dosing, targeting this pathway alone or with advanced therapies holds potential for disease-modifying asthma treatments, highlighting the need for well-designed clinical studies.

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