

Mini review

# A review of the role of high mobility group box 1 in nasal inflammation: Insights from allergic rhinitis and chronic rhinosinusitis

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**Summary.** Allergic rhinitis and chronic rhinosinusitis are highly prevalent chronic inflammatory disorders of the nasal mucosa that impair sleep, work productivity and negatively impact quality of life; and represent a considerable medical, social, and economic burden to patients and their families. Both conditions are driven by complex immune mechanisms, including epithelial barrier dysfunction, dysregulated innate and adaptive immune responses, and persistent inflammatory signaling. High mobility group box 1 (HMGB1) protein was identified as a key nuclear protein that, when released extracellularly under conditions of cellular stress or injury, acts as a potent danger-associated molecular pattern (DAMP) or alarmin that amplifies inflammation through interactions with certain receptors. Relevant publications were identified through a targeted search of PubMed and Google Scholar, using the terms HMGB1, allergic rhinitis, chronic rhinosinusitis, and nasal inflammation. This review analyzed available evidence regarding the role of HMGB1 in the pathogenesis of allergic rhinitis and chronic rhinosinusitis, emphasizing its association with disease severity, eosinophilic inflammation, and disruption of epithelial homeostasis. The identified studies found increased expression of HMGB1 in the serum, nasal tissues, and airway secretions of affected individuals, as well as enhanced activation of HMGB1-associated receptor pathways. Furthermore, this review summarizes emerging therapeutic approaches targeting HMGB1, including the use of glycyrrhetic acid, ethyl pyruvate, and resveratrol, which showed favorable anti-inflammatory effects in experimental models and early clinical settings, without significant adverse reactions. These findings suggest that inhibition of HMGB1 may represent a promising therapeutic option for patients with chronic inflammatory diseases of the upper airways. However, continued experimental and clinical research is necessary to validate these results and advance novel treatment strategies that could reduce the burden associated with these disabling conditions.

**Keywords:** allergic rhinitis, chronic rhinosinusitis, HMGB1, nasal inflammation.

## INTRODUCTION

Allergic rhinitis (AR) is a widespread chronic inflammatory disease affecting the nasal mucosa, presenting with symptoms including sneezing, nasal obstruction, excessive nasal discharge, and itching, often in combination with watery eyes and throat discomfort. AR develops as a consequence of a type I hypersensitivity response occurring in

the nasal mucosa upon contact with common aeroallergens, such as pollens from grasses and trees, dust mites, and animal-derived particles. Traditionally, AR has been divided into seasonal and perennial forms, based on the temporal distribution of symptoms (Siddiqui et al. 2022). Seasonal AR has been linked to outdoor allergens, particularly pollens from grasses and trees, while perennial AR is attributed to persistent exposure to indoor allergens throughout the year, most

commonly dust mites and animal dander. Epidemiological data indicate that AR affects approximately 5% to 50% of the global population. While past decades have shown a steady increase in prevalence, current evidence suggests that this growth has stabilized, though marked differences persist between regions. The occurrence of AR usually rises with age and is most common during young adulthood. Because it negatively influences sleep and overall quality of life, AR contributes to a considerable social and economic burden, expressed through healthcare expenses, reduced work efficiency, and increased rates of absenteeism and presenteeism (Wise et al. 2023). Individuals suffering from AR might show up to work, but their symptoms (like fatigue, congestion, and sneezing) significantly impair their focus and efficiency. It is believed that the development of AR is influenced by several factors, including compromised nasal epithelial integrity, which allows allergens to penetrate and trigger immune activation. This leads to a Th2 type of immune response, with increased production of cytokines such as IL-4, IL-5, and IL-13, which drive inflammation and promote IgE synthesis. Upon subsequent allergen exposure, mast cells are activated via IgE, releasing histamine, leukotrienes, and prostaglandins, which in turn produce the characteristic symptoms of AR (Dierick et al. 2020).

Therapeutic strategies for AR involve a broad spectrum of interventions, from patient education aimed at minimizing allergen exposure, through pharmacological treatment with intranasal corticosteroids and anti-histamines, to allergen immunotherapy, which has recently emerged as a particularly relevant option. Although these therapies can be effective in the short term, their long term outcomes are generally modest, underlining the importance of exploring new long-term treatment modalities (Ponda et al. 2023).

Chronic rhinosinusitis (CRS) represents another nasal chronic inflammatory disorder with considerable effects on individuals, by diminishing quality of life, and on society, by contributing to higher healthcare costs and decreased productivity. Recent studies have estimated the prevalence of CRS to range between approximately 5% and 15% globally (Min et al. 2025). To establish a diagnosis of CRS, symptoms must persist for a minimum of 12 consecutive weeks. Key symptoms include nasal obstruction and/or rhinorrhea, accompanied by at least two additional manifestations, such as facial pain/pressure or reduced/lost sense of smell. Furthermore, diagnosis is supported by endoscopic evidence of disease, including nasal polyps, edema, or mucopurulent secretion in the middle nasal meatus, as well as abnormal radiological findings. CRS displays considerable variation in clinical features and patterns of inflammation. Using nasal endoscopy as a basis, the condition is commonly classified into two major types: CRS without nasal polyps (CRSsNP)

and CRS with nasal polyps (CRSwNP) (Laidlaw et al. 2021). The underlying mechanisms of CRS are diverse, involving type 1 (Th1, Tc1, ILC1), type 2 (Th2, Tc2, ILC2), and type 3 (Th17, Tc17, ILC3) immune responses. Type 2 inflammation is strongly correlated with eosinophilic infiltration, nasal polyp formation, asthma comorbidity, and more severe disease. Neutrophils contribute to the pathophysiology of both eosinophilic and non-eosinophilic CRS, but are generally regarded as being especially relevant in non-eosinophilic disease variants. Inflammation driven by neutrophils is associated with poor treatment responsiveness and persistent disease, especially in Asian populations, where neutrophilic CRS is more frequently observed. Current management of CRS involves a range of therapeutic interventions, including: nasal irrigation and intranasal topical corticosteroids, antimicrobial treatment for exacerbations, surgical procedures including various types of endonasal operations, and biologic therapy, which has gained prominence in recent years. However, in spite of these interventions, CRS is frequently refractory to treatment, highlighting the need for further research to optimize therapeutic strategies (Fokkens et al. 2020).

The nasal mucosa constitutes the initial defense against airborne infections, with disturbances in the nasal microbial community having a substantial impact on both the initiation and progression of inflammatory processes in the nasal cavity. Numerous mediators participate in the inflammatory cascade that initiates and sustains inflammation, with the High mobility group box 1 (HMGB1) recently gaining increasing attention. HMGB1 is a highly conserved nuclear protein composed of 215 amino acids (~30 kDa), encoded by a gene on chromosome 13 (13q12). HMGB1 protein is present in the nuclei of all cell types, where it contributes to cellular homeostasis. In the nucleus, it acts as a non-histone chromatin-associated protein and DNA chaperone, contributing to chromosomal stabilization and the regulation of gene transcription. In response to cellular stress, under certain conditions, HMGB1 may relocate from the nucleus to the cytoplasm or be secreted into the extracellular space. HMGB1 is classified as an alarmin, and is part of a group of endogenous factors, termed endokines, that stimulate immune responses via interactions with specific receptors, including pathogen recognition receptors (PRRs) like toll-like receptors (TLRs) and receptors for advanced glycation end products (RAGE) (Ciprandi et al. 2020).

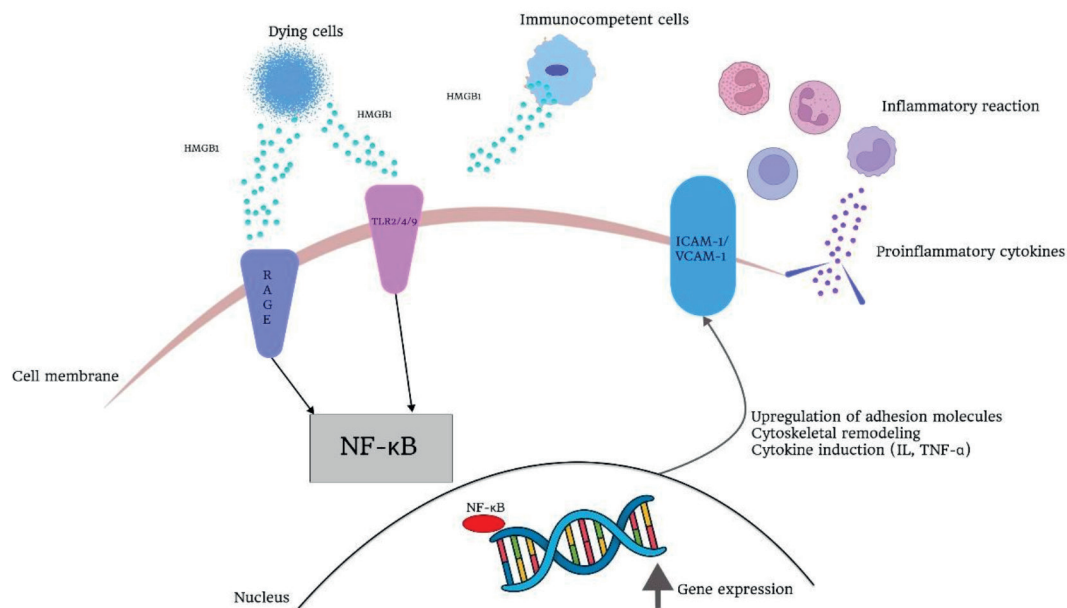
Given its pivotal role in triggering and sustaining inflammatory responses, HMGB1 has emerged as a potential early marker for various conditions associated with systemic and/or local inflammation. Numerous studies have demonstrated increased HMGB1 levels, both in circulation and affected tissues, and a positive association between HMGB1 concentration and the severity of disease. Evidence supports

the use of serum HMGB1 as a diagnostic and follow-up biomarker across various pathological conditions, including sepsis, obesity, cancer progression, and a spectrum of inflammatory and autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, vasculitis, and inflammatory bowel disease. Elevated levels of HMGB1 have been found in distinct biological specimens, including stool samples, synovial fluid, nasal lavage fluid, sputum, and cerebrospinal fluid, which has been interpreted as evidence of local synthesis at the inflammatory site. While increased HMGB1 in serum represents systemic inflammatory activity, it does not provide information regarding the initially affected organ. Local biological samples, however, frequently show an earlier and more substantial rise in HMGB1 levels than that observed in circulation. Given these characteristics, HMGB1 not only serves as a biomarker of inflammatory activity, but also represents a potential therapeutic target in a range of chronic inflammatory diseases, including those affecting the upper airways, such as AR and CRS (Colavita et al. 2020).

This review aims to elaborate and discuss the significance of HMGB1 in AR and CRS, two of the most prevalent nasal inflammatory diseases, as well as to discuss its potential utility as a target for therapeutic intervention.

## HMGB1 - MECHANISM OF ACTION IN INFLAMMATION

HMGB1 is a key regulator of both innate and adaptive immune responses, promoting immune activation in reaction to sterile or infectious stimuli. Once released into the extracellular space, HMGB1 acts as a potent damage-associated molecular pattern (DAMP) molecule, transmitting danger signals through interactions with multiple receptor families, including: RAGE, TLR2, TLR4, TLR9, CXCR4, CD24, Tim-3, IL-1R1, and Integrin/Mac-1; thereby mediating a broad spectrum of inflammatory and immune responses (Fig. 1). Translocation of HMGB1 into the extracellular space occurs primarily via two mechanisms: active secretion by immunocompetent cells and passive release from dying (apoptotic or necrotic) cells. Despite the wide range of receptors that have been proposed to bind HMGB1, only RAGE and TLR4 have been conclusively established as authentic HMGB1 receptors (Wang and Zhang 2020; Xue et al. 2021). The involvement of HMGB1 in endothelial cell activation has been highlighted in several studies, recognizing it as a pivotal step in systemic inflammatory processes and sepsis. HMGB1 upregulates adhesion molecules such as ICAM-1 and VCAM-1 on endothelial cells, enhancing leukocyte adhesion and transmigration



**Fig. 1.** Illustration of the mechanism of action of HMGB1 during an inflammatory response. The translocation of HMGB1 from the intracellular to the extracellular space occurs through two main pathways: active secretion by immunocompetent cells (such as macrophages, B cells, and T cells) and passive release from dying cells (either apoptotic or necrotic). Once in the extracellular environment, HMGB1 can bind to its receptors expressed on various cell types, including epithelial cells. By interacting with these receptors—most commonly RAGE and TLR2/4/9—HMGB1 triggers downstream signaling cascades, leading to the activation of transcription factors such as NF- $\kappa$ B, which subsequently increase the expression of pro-inflammatory genes. As a result, there is an upregulation of adhesion molecules and enhanced secretion of pro-inflammatory mediators, ultimately amplifying and sustaining the inflammatory process. (Legends: ICAM-1 - Intercellular Adhesion Molecule-1; VCAM-1 - Vascular Cell Adhesion Molecule-1; IL - interleukin; TNF- $\alpha$  - Tumor necrosis factor-alpha).

into sites of inflammation (Yang et al. 2015).

TLRs are evolutionarily conserved molecules that trigger innate immune mechanisms in response to both internal and external stimuli. When HMGB1 binds to TLR2, TLR4, or TLR9, it activates Nuclear Factor kappa B (NF- $\kappa$ B) and interferon regulatory factor (IRF) signaling cascades, leading to increased synthesis of inflammatory cytokines and chemokines (Yang et al. 2020). In a study conducted by Shimizu and colleagues (2016), it was found that binding of HMGB1 to TLR4 receptors leads to increased secretion of IL-6 and IL-8 by nasal epithelial cells, which are key mediators in the progression of inflammation.

RAGE is a transmembrane receptor of the immunoglobulin superfamily, and was the first receptor identified to interact with HMGB1 (Hori et al. 1995). HMGB1 binding with RAGE facilitates its internalization via endocytosis, enabling the delivery of HMGB1 and associated molecular complexes (e.g., with DNA, RNA, or lipopolysaccharides) into the cytoplasm. Within the cytoplasm, these complexes engage intracellular receptors such as TLR9, AIM2, or caspase-11, thereby sustaining inflammatory signaling through the activation of transcription factors, including NF- $\kappa$ B, which drives the expression of pro-inflammatory cytokines, including tumor necrosis factor (TNF- $\alpha$ ) and interleukins such as IL-6 and IL-1 $\beta$  (Singh and Agrawal 2022). Also, activation of the HMGB1-RAGE axis triggers downstream effects, such as cytoskeletal remodeling, cell adhesion, chemotaxis, proliferation and differentiation, cell death, and cross-talk with other HMGB1 receptors, including TLR4. While most researchers have concluded that HMGB1 binding to RAGE leads to NF- $\kappa$ B activation and cytokine generation, macrophages expressing both TLR4 and RAGE do not secrete cytokines upon stimulation with any HMGB1 isoform if TLR4 is absent or nonfunctional. This observation implies that direct cytokine induction by HMGB1-RAGE interactions may not occur independently of TLR4 signaling (Yang et al. 2020).

## AR AND HMGB1

As previously noted, disruption of the epithelial barrier enhances allergen penetration into the underlying mucosa, leading to monocyte activation and initiating a cascade of allergic responses. Moreover, local epithelial injury, within the skin or mucosal surfaces, promotes release of epithelial-derived cytokines, including IL-25 and IL-33, which further drives allergic inflammation and contributes to the pathogenesis of AR. Several studies have demonstrated that HMGB1 plays a role in different types of epithelial cell injury (Ohwada et al. 2021; Ma et al. 2025).

Dysregulation of the Th1/Th2 immune response in favor of Th2, is considered to be a pivotal contributor to

the immunopathogenesis of AR (Wu et al. 2023). In a study by Cavone et al. (2015), exposure of the nasal mucosa to pathogenic stimuli was shown to provoke a substantial release of HMGB1 into the extracellular environment. This process promotes eosinophil recruitment and amplifies the Th2-driven inflammatory response. In turn, Th2 activation further induces HMGB1 expression, leading to the release of numerous proinflammatory cytokines that intensify eosinophilic accumulation (Wu et al. 2023; Passali et al. 2025). Researchers from China found that levels of IL-4, IL-5, IL-13, and IL-17A were significantly elevated, whereas IL-10 was markedly reduced in nasal lavage fluid samples from patients with AR compared with healthy controls. Moreover, elevated expression levels of HMGB1, TLR2, and TLR4 were also detected in nasal brushing samples obtained from these patients, suggesting that the HMGB1-TLR signaling pathway may contribute to the dysregulated immune responses observed in AR (Zhu et al. 2020). Immunohistochemical analyses have demonstrated markedly increased HMGB1 expression in the nasal mucosa of patients with AR compared to healthy controls. Moreover, its expression appears to be closely associated with IL-33, as both molecules exhibit time- and dose-dependent upregulation following stimulation with allergens (Zhong et al. 2022).

Previous studies have demonstrated that the overexpression of HMGB1 is closely associated with disease severity and poor prognosis in various inflammatory and neoplastic disorders. Serum HMGB1 levels were significantly elevated in children with AR (Xing and Wang 2023). Moreover, individuals with higher HMGB1 expression exhibited markedly increased scores on the Rhinoconjunctivitis Quality of Life Questionnaire, indicating a strong association between HMGB1 levels and disease burden. Another study conducted in children demonstrated that those with AR exhibited significantly elevated concentrations of HMGB1 in sputum, plasma, and nasal lavage fluid compared with non-allergic controls (Salpietro et al. 2013). Similarly, research on serum biomarkers in patients with AR has revealed that increased serum concentrations of cytokines and inflammatory mediators, such as IL-1 $\beta$ , IL-17, and TNF, may serve as valuable indicators of AR and correlate positively with disease severity (Bayrak Degirmenci et al. 2018).

Collectively, these findings underscore the pivotal role of HMGB1 in immune regulation and the pathogenesis of AR.

## CRS AND HMGB1

Given the substantial differences in the underlying pathophysiological mechanisms across CRS endotypes, for otolaryngology practitioners it is essential to differentiate between the phenotypic presentations of chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis



with nasal polyps (CRSwNP). Accordingly, the following section will outline the key distinguishing features of these entities, with a particular focus on the role of HMGB1 in the inflammatory cascade (Passali et al. 2025).

Evidence from the literature indicate that HMGB1 expression in CRSwNP is predominantly localized within nasal polyp tissue, rather than being restricted to epithelial cells (Bellussi et al. 2012). Notably, HMGB1 levels show a strong positive correlation with eosinophilic infiltration, with significantly higher expression detected in eosinophilic CRSwNP (ECRSwNP) compared with control subjects. Conversely, in non-eosinophilic CRSwNP (NECRSwNP), neither HMGB1 protein levels nor HMGB1 mRNA expression differ significantly from those of healthy controls, suggesting that HMGB1 upregulation is particularly associated with eosinophil-driven inflammatory disease (Chen et al. 2014; Dzaman et al. 2015a). Additionally, another study reported that HMGB1 levels in both polyp exudates and nasal lavage fluids effectively distinguish ECRSwNP from NECRSwNP, with significantly higher HMGB1 concentrations observed in both sample types from patients with ECRSwNP (Min and Kim 2021).

In a proteomic analysis of CRSsNP using a highly multiplexed approach, HMGB1 was among the examined proteins, and was found to be significantly upregulated in the nasal mucus of CRSsNP patients (Pesold et al. 2023). HMGB1 levels may also serve as an indicator of disease severity. Comparison with the Lund-Mackay score (radiology-based system for grading CRS severity using sinus CT scans) revealed that cytoplasmic HMGB1 levels were higher in tissues from patients with elevated Lund-Mackay scores compared to those with lower scores. Notably, the presence or absence of nasal polyps was not significantly associated with HMGB1 expression (Min et al. 2015).

In the context of CRS, multiple studies have demonstrated a marked upregulation of HMGB1 receptors. RAGE expression correlated positively with clinical measures of disease burden, such as radiologic severity (Lund-Mackay score), polyp dimensions, and the frequency of previous surgical procedures (Dzaman et al. 2015a). RAGE immunorexpression was markedly elevated in CRSsNP patients, compared to healthy controls. Moreover, RAGE levels correlated with the number of tissue-infiltrating lymphocytes and showed a positive association with disease severity, as well as a history of allergic conditions (Dzaman et al. 2015b). Disrupted RAGE–HMGB1 signaling may undermine mucosal defense and facilitate antigen entry, driving ongoing sinonasal inflammation.

TLRs are key mediators of innate immunity in the sinonasal mucosa. Evidence indicates that nasal epithelial cells express TLR3, TLR7, and TLR9 at the mRNA level, support-

ing their role in the recognition of pathogens and initiation of immune responses (Tengroth et al. 2014). TLR4 and TLR9 are present in the sinus mucosa of both CRS patients and healthy individuals. Notably, the expression of these receptors is higher in patients compared with controls, with TLR4 exhibiting greater levels than TLR9, although this difference did not reach statistical significance (Taziki et al. 2019). These findings suggest that upregulation of TLRs in diseased sinus tissue may contribute to enhanced immune responsiveness and inflammation in CRS.

## HMGB1 AS A TARGET FOR THERAPY IN AR AND CRS

In recent years, multiple studies have investigated HMGB1 as a potential therapeutic target in AR and CRS. The predominant therapeutic strategy under consideration involves neutralizing extracellular HMGB1 after its release. This approach is preferred over targeting its receptors (such as RAGE and TLRs) or preventing HMGB1 secretion from activated immune cells, as receptor blockade or inhibition of upstream release mechanisms may interfere with other essential protective pathways that rely on these receptors and signaling systems (Ciprandi et al. 2020). HMGB1 targeted therapies can generally be divided into endogenous and exogenous inhibitory strategies. Endogenous inhibitors include neutralizing antibodies, acute-phase proteins, and certain endogenous hormones. Exogenous inhibitors refer to plant derived compounds and herbal extracts, as well as specific bioactive constituents (Table 1) like glycyrrhizin and resveratrol (RSV). Among these, ethyl pyruvate (EP), glycyrrhizic acid (GA), and glycyrrhetic acid (GTA) have attracted particular interest in recent research on AR (Wu et al. 2023).

Glycyrrhizin is a naturally occurring glycosidic alkaloid abundantly present in the roots of *Glycyrrhiza glabra*, the botanical source of licorice. Structurally, it consists of one GTA (responsible for its biological activity) linked to two glucuronic acid molecules. GTA suppresses the chemotactic and mitogenic activities of HMGB1 by interacting with hydrophobic residues located around the binding pockets in its A and B box domains (Bellussi et al. 2017). GA and GTA demonstrate both anti-inflammatory and anti-allergic properties. They selectively target extracellular HMGB1, suppressing its cytokine activity by promoting HMGB1 clearance. Furthermore, in rhinitis models, GTA has been reported to reduce HMGB1 secretion by enhancing the expression of Sirtuin 6 (Sirt6), a member of the sirtuin family, which plays a key role in processes such as aging, DNA repair, metabolism, inflammation, and oncogenesis. Notably, Sirt6 expression is reduced in CRSwNP tissue, suggesting that GTA-mediated modulation of Sirt6 may offer therapeutic benefits for pa-

tients with CRSwNP (Chen et al. 2017; Wu et al. 2023). GTA demonstrates a favorable safety profile. Intravenous administration at a dose of 240 mg, three times per week for four weeks, has been reported without any adverse effects. In addition, multiple studies indicate that glycyrrhizin shows no cytotoxicity even at high concentrations, and is well tolerated in both animal models and humans (Ciprandi et al. 2020).

Ethyl pyruvate, a more stable ester derivative of pyruvic acid, the terminal product of glycolysis, exhibits a prolonged half-life and is categorized as an endogenous inhibitor. Due to its structural similarity to pyruvate, EP functions as a protective antioxidant, helping to reduce reactive oxygen species-mediated injury in conditions such as endotoxemia, sepsis, and other inflammatory disorders (Xue et al. 2021). In an experimental model it was shown that EP markedly suppresses multiple hallmarks of allergic inflammation, including airway eosinophil accumulation, Th2 cytokine production, total IgE levels, goblet cell hyperplasia, and nasal symptom severity (Chen et al. 2015). Various mechanisms contribute to the anti-inflammatory actions of EP, one of which involves suppression of HMGB1 release. EP treatment has been shown to markedly reduce HMGB1 expression and prevent its translocation in a dose-dependent fashion (Bellusi et al. 2017).

Resveratrol (RSV) is a naturally occurring polyphenol commonly present in high concentrations in peanuts, grapes, and various berries. Initially identified for its anti-tumor properties, it was later recognized as an important

regulator of inflammatory processes. In patients with AR, administration of RSV has been shown to markedly alleviate nasal symptoms by reducing serum levels of pro-inflammatory cytokines, including IL-4 and TNF- $\alpha$ . RSV is a well-known activator of silent information regulator 1 (SIRT1), an anti-inflammatory mediator that plays a pivotal role in the progression of AR (Lv et al. 2018). In a study conducted on ovalbumin-induced AR in mice, RSV treatment was found to down-regulate HMGB1 and TLR4 expression, while up-regulating SIRT1 levels in the nasal mucosa. These findings suggest that SIRT1 may play a regulatory role in modulating HMGB1 and TLR4 expression, thereby contributing to protection against the progression of AR (Li et al. 2020).

## CONCLUSION

Allergic rhinitis and chronic rhinosinusitis constitute a substantial public health challenge globally, both in terms of health burden and economic impact. Their high prevalence contributes to marked functional impairment in daily tasks, reduced quality of life, and increased work absenteeism with subsequent loss of productivity. HMGB1, a representative protein of the DAMP family, has been identified as an important mediator in the initiation and maintenance of inflammatory processes in numerous disorders, including chronic inflammatory diseases of the nasal mucosa such as AR and CRS. Targeting HMGB1 may offer a promising and novel therapeutic strategy for individuals suffering from AR

**Table 1.** Proposed HMGB1 inhibitors: potential therapeutic agents.

Inhibitor	Naturally occurring in	Mechanism of action	Applied on humans	References
Glycyrrhizin (glycyrrhizic acid and glycyrrhetic acid)	Licorice plant ( <i>Glycyrrhiza glabra</i> )	<ul style="list-style-type: none"> <li>- Inhibition of HMGB1 release by stimulated macrophages.</li> <li>- Blocking extracellular HMGB1 from its receptors by directly binding to A box and B box domains.</li> <li>- Promoting HMGB1 clearance from extracellular space.</li> </ul>	<ul style="list-style-type: none"> <li>- Intravenous 240 mg, 3×/week for 4 weeks, no adverse effects reported.</li> <li>- Intranasal treatment reduced HMGB1 in AR nasal fluids, comparable to budesonide.</li> </ul>	Bellusi et al. 2017; Sabbadin et al. 2019; Ciprandi et al. 2020; Xue et al. 2021
Ethyl pyruvate	Low natural occurrence, usually synthesized for research purposes	<ul style="list-style-type: none"> <li>- Suppression of HMGB1 release.</li> <li>- Interference with the NF-<math>\kappa</math>B pathway activation, thereby limiting subsequent cytokine release.</li> </ul>	One clinical trial examining the safety and prevention of complications in cardiac surgery patients on cardiopulmonary bypass, ended in Phase II: safe in healthy and patient groups, no efficacy vs. Placebo.	Bellusi et al. 2017; Koprivica et al. 2022
Resveratrol	Grapes, peanuts, blueberries, cocoa	- Down-regulation of HMGB1 and TLR4 expression.	~200 studies over 20 years across $\geq 24$ conditions; no consensus regimen; generally well-tolerated up to 1 g/day.	Li et al. 2020; Brown et al. 2024

and CRS. GTA acts by neutralizing extracellular HMGB1, thereby suppressing its chemotactic and proliferative activity. Clinical use of GTA for the management of AR is associated with a favorable safety profile, with no reported local or systemic adverse effects in either pediatric or adult populations. Given these encouraging findings, further clinical and experimental investigations in this field are warranted, with the goal of alleviating the significant burden associated with these disorders, which extend beyond the scope of otorhinolaryngology alone.

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