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Efficacy of Pharmacological and Bioactive Compounds on Serum Ovalbumin-Specific Immunoglobulin E and Nasal Symptom Scores in Ovalbumin-Induced Allergic Rhinitis Animal Models: A Systematic Review and Meta-Analysis

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Abstract

Allergic rhinitis (AR) is a highly prevalent immunoglobulin E (IgE)-mediated inflammatory disease of the nasal mucosa. Ovalbumin (OVA)-induced AR animal models are widely used to evaluate potential therapeutic agents; however, no quantitative synthesis of treatment effects across pharmacological interventions has been performed. This study aimed to systematically review and meta-analyse the effects of pharmacological and bioactive interventions on serum OVA-specific IgE levels, nasal rubbing scores, and nasal sneezing scores in OVA-induced AR animal models. PubMed, EMBASE, and Scopus were searched from inception through 22 May 2026. Eligible studies were in vivo experimental studies using OVA-sensitised and intranasally challenged rodent models with at least one pharmacological intervention and an untreated or vehicle control group. Risk of bias was assessed using the SYRCLE tool. Standardised mean differences (SMDs) were pooled using random-effects models with the restricted maximum likelihood (REML) estimator and the Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustment. Analyses were conducted in R using the metafor package. Fourteen intervention studies met the inclusion criteria. Pharmacological and bioactive interventions significantly reduced serum OVA-specific IgE levels (pooled SMD = −3.03; 95% CI: −4.77 to −1.28; I^2 = 78.1%), nasal rubbing scores (pooled SMD = −5.24; 95% CI: −7.17 to −3.31; I^2 = 80.2%), and nasal sneezing scores (pooled SMD = −4.29; 95% CI: −5.79 to −2.78; I^2 = 78.5%). Substantial heterogeneity was observed across all outcomes. Leave-one-out sensitivity analyses confirmed the robustness and directionality of the pooled estimates. Pharmacological and bioactive interventions consistently and significantly attenuated serum OVA-specific IgE levels and nasal symptom scores in OVA-induced AR animal models.

INTRODUCTION

Allergic rhinitis (AR) is a chronic inflammatory disorder of the nasal mucosa mediated by immunoglobulin E (IgE) in response to allergen exposure (Bousquet et al., 2008; Skoner, 2001). The condition affects approximately 10–40% of the global population and is characterised by nasal congestion, rhinorrhoea, sneezing, and pruritus, collectively imposing a substantial burden on quality of life and healthcare expenditure (Brozek et al., 2017; Wheatley & Togias, 2015). The pathophysiology of AR involves allergen-driven T-helper 2 (Th2)

polarisation, resulting in elevated production of interleukin (IL)-4, IL-5, and IL-13, which promote B-cell class switching to IgE, eosinophilic infiltration, and mast cell degranulation (Galli & Tsai, 2012; Pawankar et al., 2011). Despite the availability of antihistamines, intranasal corticosteroids, and allergen immunotherapy, a considerable proportion of patients experience inadequate symptom control, necessitating the continued exploration of novel therapeutic strategies (Seidman et al., 2015).

Ovalbumin (OVA)-induced AR models in rodents represent the most widely utilised preclinical platform for evaluating candidate anti-allergic agents (Shin et al., 2009; Patel et al., 2014). These models reliably reproduce the cardinal features of human AR, including OVA-specific IgE elevation, nasal mucosal eosinophilia, and behavioural nasal symptoms such as rubbing and sneezing upon intranasal allergen challenge (Nabe, 2020). Over the past decade, numerous individual studies have examined the efficacy of diverse pharmacological compounds, ranging from natural products to synthetic agents. However, the existing literature remains fragmented, with considerable heterogeneity in study design, dosing regimens, outcome measurements, and animal strains across investigations. To date, no systematic review or meta-analysis has quantitatively synthesised the treatment effects of pharmacological interventions on OVA-specific IgE and nasal symptom scores in OVA-induced AR animal models.

The novelty of this systematic review and meta-analysis lies in four key aspects. First, this study represents the first comprehensive quantitative synthesis of pharmacological and bioactive treatment effects on both immunological (OVA-specific IgE) and behavioural (nasal rubbing and sneezing) outcomes in OVA-induced AR animal models. Second, this review applies rigorous meta-analytic methods, including the Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustment for small-sample bias and prediction intervals to characterise the expected range of true effects. Third, this study systematically assesses risk of bias using the SYRCLE tool, specifically designed for animal intervention studies. Fourth, this review identifies critical methodological gaps in the existing preclinical literature and provides recommendations for improving study design and reporting.

This systematic review and meta-analysis was therefore designed to address this evidence gap by comprehensively evaluating the efficacy of pharmacological and bioactive compounds on serum OVA-specific IgE concentrations and nasal symptom parameters — specifically rubbing and sneezing frequency — in OVA-induced AR animal models. By synthesising data across multiple compounds, species, and outcome domains using standardised effect size estimation, this review aims to provide a rigorous quantitative foundation for prioritising candidate compounds for translational development and to identify critical methodological gaps in the existing preclinical literature.

METHOD

Search Strategy

A systematic literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines (Page et al., 2021). Three electronic databases of PubMed, EMBASE, and Scopus were searched from inception through 22 May 2026 without language restriction. The search strategy combined medical subject headings and free-text terms encompassing the following concepts: (1) allergic rhinitis or rhinitis or nasal allergy or hay fever; (2) ovalbumin or OVA; (3) natural compound or phytochemical or flavonoid or polyphenol or terpenoid or herbal or plant extract; and (4) animal or mouse or murine or rat. Boolean operators were employed to combine search strings. Reference lists of included studies and relevant review articles were manually screened to identify additional eligible records.

Eligibility Criteria

Studies were selected according to predefined eligibility criteria structured using the Population, Intervention, Comparison, and Outcome (PICO) framework. The population comprised mice or rats with OVA-induced allergic rhinitis established through systemic sensitization (intraperitoneal or subcutaneous OVA injection) followed by intranasal OVA challenge. The intervention included any active pharmacological or bioactive treatment administered to OVA-sensitized and challenged animals; conventional positive-control agents were eligible only when they were analyzed as active pharmacological intervention arms and clearly contrasted against an OVA-induced AR control. The comparator was an OVA-induced AR vehicle-treated or untreated control group. The primary outcome was serum OVA-specific IgE or anti-OVA IgE levels. Secondary outcomes included nasal rubbing frequency and nasal sneezing frequency.

Inclusion criteria required that studies be original, peer-reviewed, in vivo experimental animal studies utilizing an OVA sensitization and intranasal OVA challenge protocol, reporting quantitative data on at least one of the predefined outcomes, and including a concurrent untreated or vehicle control group. Studies were excluded if they were not in vivo experimental animal studies, were conference or meeting abstracts only, used asthma-only models without allergic rhinitis or nasal outcomes, lacked an OVA sensitization and intranasal OVA challenge protocol, or did not include a relevant intervention or treatment group. Two independent reviewers screened titles, abstracts, and full texts; disagreements were resolved by consensus or by consultation with a third reviewer.

Data Extraction

Two reviewers independently extracted data using a standardized electronic workbook. The following variables were recorded for each included study: first author and year of publication, country and institutional setting, animal species and strain, sex and age or weight, sample size per group, ovalbumin sensitization and challenge protocols, intervention identity and dose, route and duration of administration, comparator identity, and all reported outcomes with corresponding mean values, error type (standard deviation or standard error of the mean), sample sizes, and units. For studies reporting outcome data only in graphical format, values were extracted through systematic visual approximation from published figures with documentation of the estimation procedure. Standard errors of the mean were converted to standard deviations using the formula: standard deviation equals standard error of the mean multiplied by the square root of the sample size. When multiple treatment doses shared a single control group, the control group sample size was appropriately split across comparisons to avoid double-counting. Discrepancies between reviewers were resolved by discussion and consensus.

Risk of Bias Assessment

Risk of bias was evaluated using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Risk of Bias tool, which is specifically designed for animal intervention studies (Hooijmans et al., 2014). The tool comprises ten domains: sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers, random outcome assessment, blinding of outcome assessor, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain was rated as low risk of bias (+), unclear risk of bias (?), or high risk of bias (–). Two reviewers independently assessed risk of bias; discrepancies were resolved through discussion.

Statistical Analysis

All meta-analyses were performed using R (version 4.6) with the metafor package (version 4.4) and the meta package (Viechtbauer, 2010; Balduzzi et al., 2019). Treatment effects were expressed as standardized mean differences (SMDs) with 95% confidence intervals (CIs). The SMD was calculated as Hedges' g to correct for small-sample bias. A

negative SMD indicated a reduction in the outcome favoring the intervention group relative to the OVA-induced AR control.

Between-study heterogeneity was estimated using the restricted maximum likelihood (REML) estimator for the variance component τ^2. The Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustment was applied to the confidence intervals of the pooled SMD to provide more adequate coverage when the number of studies is small or heterogeneity is substantial (Hartung & Knapp, 2001; Sidik & Jonkman, 2002). Statistical heterogeneity was quantified using the I^2 statistic and the Cochran Q test. I^2 values of 25%, 50%, and 75% were considered indicative of low, moderate, and high heterogeneity, respectively (Higgins et al., 2003).

Subgroup analyses were performed by AR model category as displayed in the forest plots (OVA models vs. AR/allergy-specific models) where sufficient data permitted. Sensitivity analyses were conducted using a leave-one-out approach, in which each comparison was sequentially removed and the pooled SMD was recalculated to evaluate the influence of individual comparisons on the overall estimate; the leave-one-out figures present common-effect recalculations, whereas the primary pooled estimates use random-effects HKSJ models. Prediction intervals were calculated to characterize the expected range of true effects in future similar studies. Statistical significance was defined as a two-sided p-value < 0.05.

RESULT AND DISCUSSION

Study selection

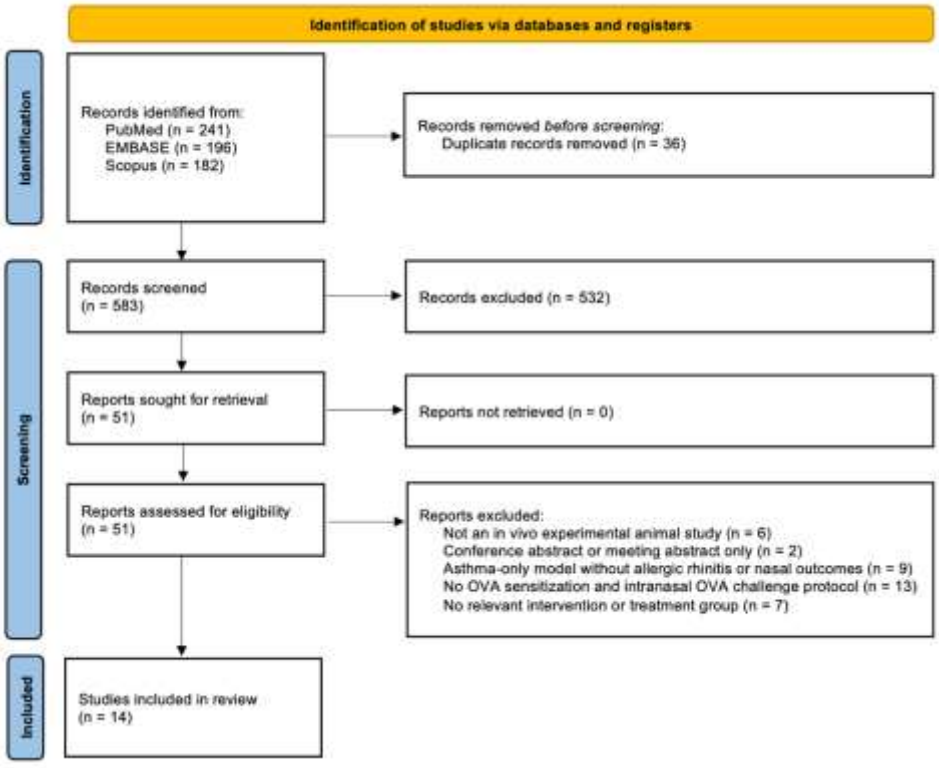

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Flow Diagram

The database search retrieved 619 records: 241 from PubMed, 196 from EMBASE, and 182 from Scopus. After removal of 36 duplicate records, 583 unique records were screened by title and abstract, of which 532 were excluded. The remaining 51 reports were sought for full-text retrieval, and all were successfully obtained. Following full-text assessment for eligibility, 36 reports were excluded for the following reasons: not an in vivo experimental animal study

(n = 6), conference abstract or meeting abstract only (n = 2), asthma-only model without allergic rhinitis or nasal outcomes (n = 9), no OVA sensitization and intranasal OVA challenge protocol (n = 13), and no relevant intervention or treatment group (n = 7). A total of 14 studies met all inclusion criteria and were included in the qualitative and quantitative synthesis. The PRISMA 2020 flow diagram is presented in Figure 1.

The 14 included intervention studies were published between 2015 and 2022 and originated from China (n = 6), the Republic of Korea (n = 5), India (n = 1), Turkey (n = 1), and one Republic of Korea/China collaborative study (n = 1). Thirteen studies used mouse models, predominantly BALB/c strains, while one study (Kaya 2019) employed Sprague-Dawley rats. The interventions comprised a heterogeneous group of pharmacological and bioactive compounds, including curcumin, skullcapflavone II, apigenin, wogonin, D-pinitol, artemisinin, α-lipoic acid, piperine, gami-hyunggyeyeongyotang (a traditional Korean herbal formulation), Hizikia fusiformis extract, misoprostol, mangiferin, tanshinone IIA, and chlorogenic acid. Sample sizes ranged from 4 to 10 animals per group where reported; Li 2018 did not clearly report animal n per group. Administration routes included oral gavage, intraperitoneal injection, intranasal delivery, and oral administration. Doses varied widely across studies. All included intervention studies utilized an OVA sensitization and intranasal OVA challenge protocol. Detailed baseline characteristics are summarized in Table 1.

Risk of bias

Risk of bias assessment using the SYRCLE tool revealed that the majority of included studies had an unclear risk of bias across most domains. All studies except one (Aswar 2015) reported baseline characteristics comparably (rated as low risk). Sequence generation was rated as unclear in all 14 studies, as none provided explicit descriptions of randomization methods. Allocation concealment, random housing, blinding of caregivers, random outcome assessment, and blinding of outcome assessors were rated as unclear in the majority of studies due to insufficient reporting. Incomplete outcome data were rated as low risk in 13 of 14 studies and unclear in one study (Li 2018), while selective outcome reporting was rated as low risk in all 14 studies. Other sources of bias were variable, with some studies rated as low risk, some as unclear, and Li 2018 rated as high risk. The complete SYRCLE risk of bias summary is presented in Table 1.

Table 1. Baseline Characteristics of Included Intervention Studies

Study ID	Compound	Species (Strain)	Sex	n	Model	Route	Dose(s)	Country
Zhang 2015	Curcumin	Mouse (BALB/c)	Female	7/group	OVA i.p. + i.n.	Gavage	100, 200 mg/kg	China
Bui 2017	Skullcapflavone II	Mouse (BALB/c)	Male	6/group	OVA i.p. + i.n.	Oral	2.5, 10 mg/kg/day	Republic of Korea
Chen 2020	Apigenin	Mouse (BALB/c)	Male	4–6/group	OVA i.p. + i.n.	Intraperitoneal	5, 10, 20 mg/kg	China
Kim 2018	Wogonin	Mouse (BALB/c)	Female	7/group	OVA i.p. + i.n.	Oral	10, 30 mg/kg	Republic of Korea
You 2021	D-Pinitol	Mouse (BALB/c)	Male	4–6/group	OVA i.p. + i.n.	Oral	5, 10, 20 mg/kg	China
Li 2018	Artemisinin	Mouse (BALB/c)	Female	NR	OVA i.p. + i.n.	Intranasal	1, 10, 100 mg/kg	China

Nguyen 2020	α-Lipoic acid	Mouse (BALB/c)	Male	6/group	OVA i.p. + i.n.	Oral	2, 10, 50 mg/kg	Republic of Korea
Aswar 2015	Piperine	Mouse (Swiss albino)	NR	6/group	OVA i.p. + i.n.	Oral	10, 20, 40 mg/kg	India
Im 2016	Gami-hyunggyeyeongyotang	Mouse (BALB/c)	Female	8/group	OVA i.p. + i.n.	Oral	134 mg/kg	Republic of Korea
Zhang 2019	Hizikia fusiformis extract	Mouse (BALB/c)	Female	9–10/group	OVA i.p. + i.n.	Intraperitoneal	300–600 mg/kg	Republic of Korea/China
Kaya 2019	Misoprostol	Rat (Sprague-Dawley)	Male	5/group	OVA i.p. + i.n.	Oral	100 μg/kg	Turkey
Piao 2020	Mangiferin	Mouse (BALB/c)	Male	6/group	OVA i.p. + i.n.	Oral	5, 20 mg/kg	Republic of Korea
Chen 2022	Tanshinone IIA	Mouse (BALB/c)	Male	10/group	OVA i.p. + i.n.	Intraperitoneal	10 mg/kg/day	China
Dong 2020	Chlorogenic acid	Mouse (BALB/c)	Male	10/group	OVA i.p. + i.n.	Oral gavage	50, 100, 200 mg/kg	China

OVA = ovalbumin; i.p. = intraperitoneal; i.n. = intranasal; NR = not reported; Chen 2020 and You 2021 reported variable sample sizes across outcome domains (n = 4–6 for biochemical outcomes; lower n for selected histology or ultrastructure endpoints); Li 2018 did not explicitly report animal n per group and described results as from at least three separate tests; Aswar 2015 used Swiss albino mice; all other mouse studies used BALB/c mice except where stated; Kaya 2019 used Sprague-Dawley rats and was the only rat model among included intervention studies; GMHGYGT = Gami-hyunggyeyeongyotang (traditional Korean herbal formulation); AR = allergic rhinitis; d = day(s); F = female; M = male; Tx = treatment.

Table 2. Risk of Bias Summary Using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Tool

Study	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding caregivers	Random outcome assessment	Blinding outcome assessor	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Zhang 2015 (Curcumin)	?	+	?	?	?	?	?	+	+	?
Bui 2017 (SCFII)	?	+	?	?	?	?	?	+	+	+
Chen 2020 (Apigenin)	?	+	?	?	?	?	?	+	+	?
Kim 2018 (Wogonin)	?	+	?	?	?	?	?	+	+	?

You 2021 (D-Pinitol)	?	+	?	?	?	?	?	+	+	?
Li 2018 (Artemisinin)	?	+	?	?	?	?	?	?	+	–
Nguyen 2020 (α-Lipoic acid)	?	+	?	?	?	?	?	+	+	+
Aswar 2015 (Piperine)	?	?	?	?	?	?	?	+	+	?
Im 2016 (GMHGYGT)	?	+	?	?	?	?	?	+	+	+
Zhang 2019 (H. fusiformis)	?	+	?	?	?	?	+	+	+	?
Kaya 2019 (Misoprostol)	?	+	?	?	?	?	+	+	+	?
Piao 2020 (Mangiferin)	?	+	?	?	?	?	?	+	+	+
Chen 2022 (Tanshinone IIA)	?	+	?	?	?	?	?	+	+	+
Dong 2020 (Chlorogenic acid)	?	+	?	?	?	?	?	+	+	?

Legend: + = Low risk of bias; ? = Unclear risk of bias; – = High risk of bias

Serum OVA-Specific IgE

Eight studies contributing eight comparisons from both OVA model and AR/allergy model subgroups contributed data for the meta-analysis of serum OVA-specific IgE. In the OVA model subgroup (6 comparisons), the pooled SMD under the random-effects model (HKSJ) was −3.15 (95% CI: −5.15 to −1.15; $I^2 = 74.3\%$; $\tau^2 = 2.4857$; heterogeneity $p = 0.0016$). In the AR/allergy model subgroup (2 comparisons), the pooled SMD (HKSJ) was −2.84 (95% CI: −33.95 to 28.26; $I^2 = 88\%$; $\tau^2 = 10.6418$; heterogeneity $p = 0.0039$), indicating an imprecise subgroup estimate with a confidence interval crossing the null. The overall pooled SMD across all comparisons under the random-effects model (HKSJ) was −3.03 (95% CI: −4.77 to −1.28). The common-effect model yielded a pooled SMD of −2.05 (95% CI: −2.57 to −1.52). Overall heterogeneity was substantial ($I^2 = 78.1\%$; $\tau^2 = 3.1798$; $p < 0.0001$). The prediction interval ranged from −7.57 to 1.52. The test for subgroup differences was significant under the common-effect model ($\chi^2 = 4.21$, df = 1, $p = 0.0401$) but not under the random-effects model ($\chi^2 = 0.01$, df = 1, $p = 0.9061$). Leave-one-out sensitivity analysis using common-effect recalculations demonstrated that the pooled SMD remained significant ($p < 0.0001$) regardless

of which comparison was omitted, with point estimates ranging from −1.85 to −2.48. The forest plot and leave-one-out analysis are presented in Figure 2.

Nasal Rubbing

Six studies contributing 12 comparisons from AR model and OVA model subgroups were included in the meta-analysis of nasal rubbing scores. In the AR model subgroup (2 comparisons), the pooled SMD (HKSJ) was −6.64 (95% CI: −19.67 to 6.40; $I^2 = 0\%$; $\tau^2 = 0$; heterogeneity $p = 0.3673$), indicating an imprecise subgroup estimate with a confidence interval crossing the null. In the OVA model subgroup (10 comparisons), the pooled SMD (HKSJ) was −5.01 (95% CI: −7.33 to −2.70; $I^2 = 81.2\%$; $\tau^2 = 6.7651$; heterogeneity $p < 0.0001$). The overall pooled SMD under the random-effects model (HKSJ) was −5.24 (95% CI: −7.17 to −3.31). The common-effect model yielded a pooled SMD of −3.72 (95% CI: −4.27 to −3.17). Overall heterogeneity was substantial ($I^2 = 80.2\%$; $\tau^2 = 6.0100$; $p < 0.0001$). The prediction interval ranged from −10.92 to 0.44. The test for subgroup differences was significant under the common-effect model ($\chi^2 = 7.01$, df = 1, $p = 0.0081$) but not under the random-effects model ($\chi^2 = 1.25$, df = 1, $p = 0.2626$). Leave-one-out sensitivity analysis using common-effect recalculations confirmed robustness, with all pooled estimates remaining significant ($p < 0.0001$) upon sequential omission (SMD range: −3.39 to −4.21). The forest plot and leave-one-out analysis are presented in Figure 3.

Nasal Sneezing

Four studies contributing 14 comparisons from AR model and OVA model subgroups were included in the meta-analysis of nasal sneezing scores. In the AR model subgroup (4 comparisons from Aswar 2015), the pooled SMD (HKSJ) was −7.09 (95% CI: −9.08 to −5.11; $I^2 = 0\%$; $\tau^2 = 0$; heterogeneity $p = 0.6591$). In the OVA model subgroup (10 comparisons), the pooled SMD (HKSJ) was −3.17 (95% CI: −4.60 to −1.74; $I^2 = 71.5\%$; $\tau^2 = 2.0154$; heterogeneity $p = 0.0002$). The overall pooled SMD under the random-effects model (HKSJ) was −4.29 (95% CI: −5.79 to −2.78). The common-effect model yielded a pooled SMD of −2.78 (95% CI: −3.22 to −2.35). Overall heterogeneity was substantial ($I^2 = 78.5\%$; $\tau^2 = 4.7765$; $p < 0.0001$). The prediction interval ranged from −9.22 to 0.65. The test for subgroup differences was significant under both the common-effect model ($\chi^2 = 27.41$, df = 1, $p < 0.0001$) and the random-effects model ($\chi^2 = 19.52$, df = 1, $p < 0.0001$). Leave-one-out sensitivity analysis using common-effect recalculations confirmed that all pooled estimates remained significant ($p < 0.0001$) upon sequential omission (SMD range: −2.71 to −3.13). The forest plot and leave-one-out analysis are presented in Figure 4.

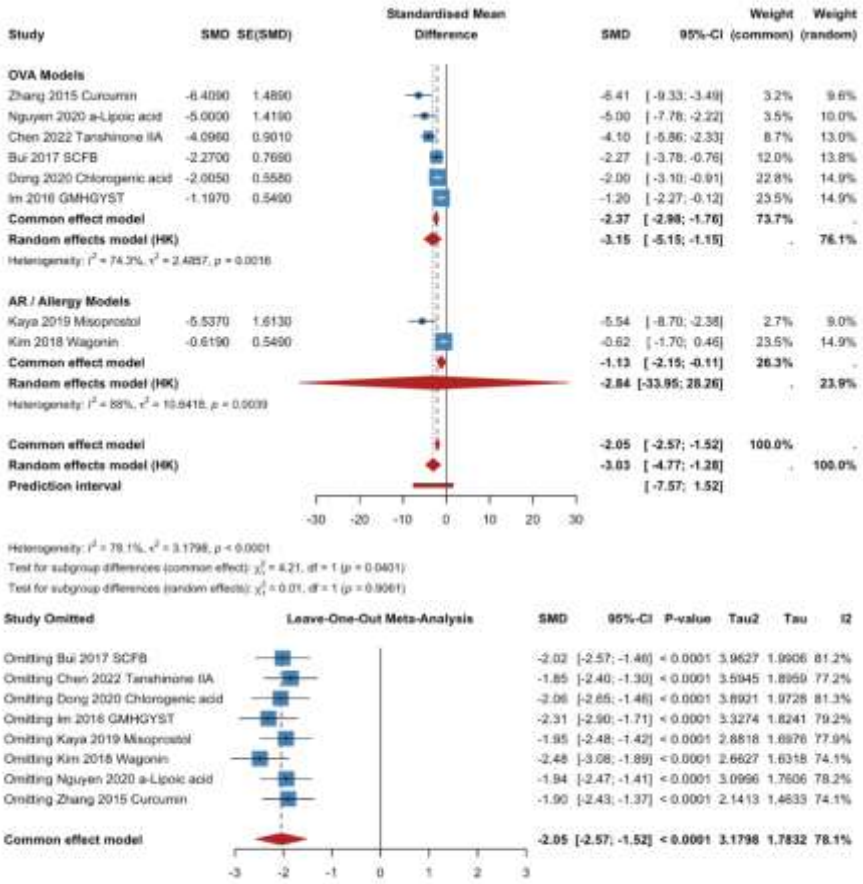

Figure 2. Meta-analysis for Pooled Standardized Mean Difference for Serum OVA-Specific IgE.

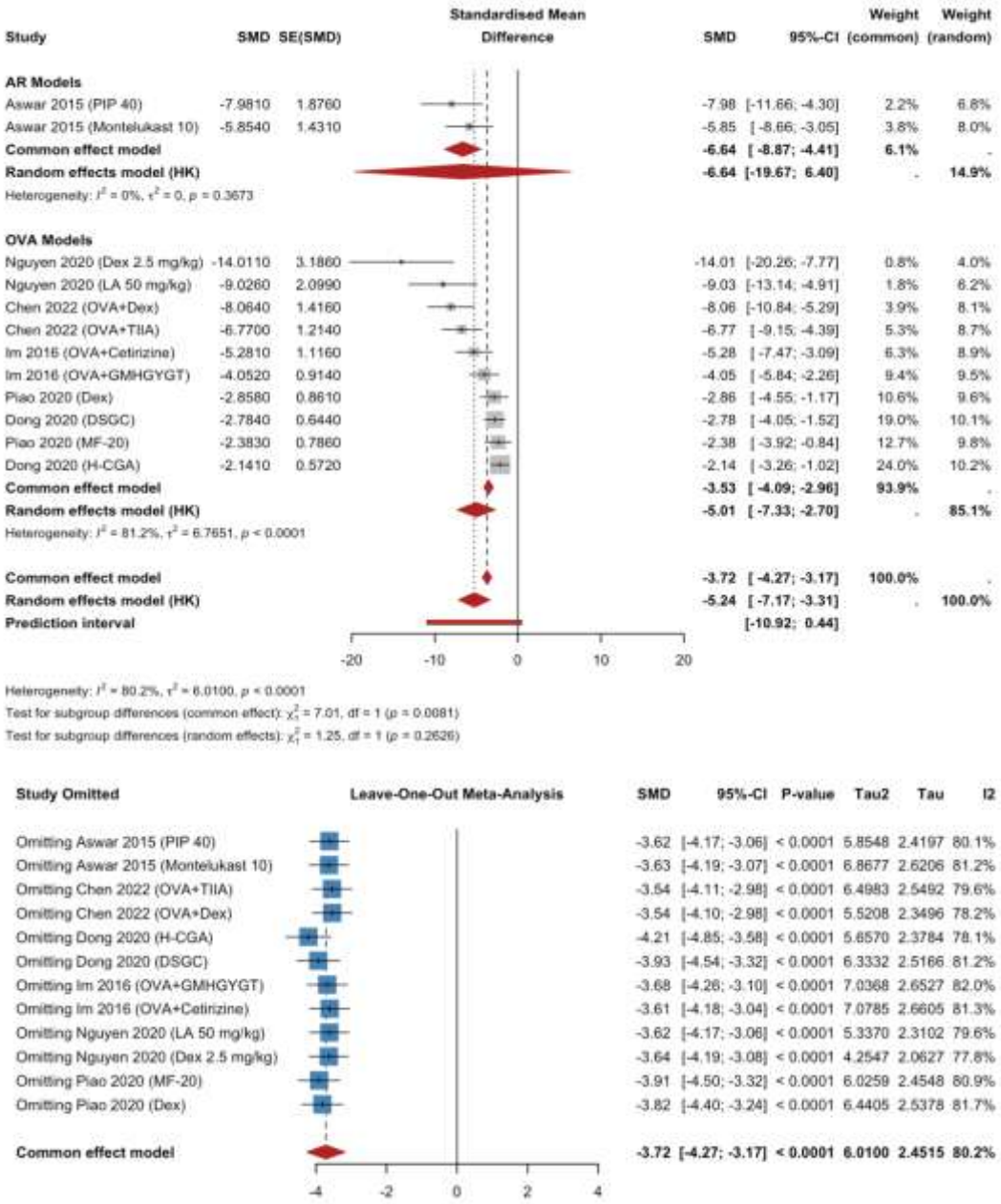

Figure 3. Meta-analysis for Pooled Standardized Mean Difference for Nasal Rubbing.

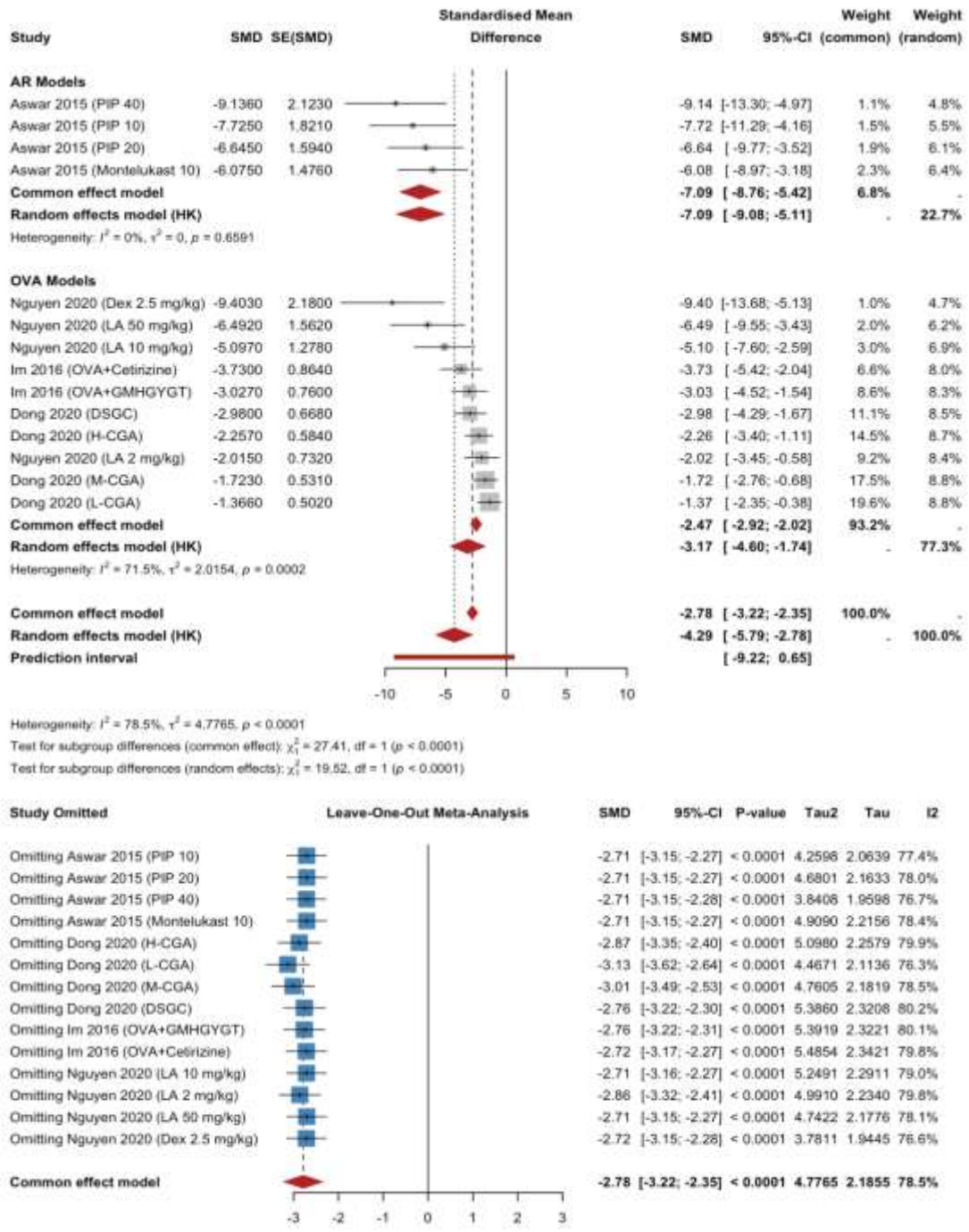

Figure 4. Meta-analysis for Pooled Standardized Mean Difference for Nasal Sneezing.

This systematic review and meta-analysis synthesised data from 14 preclinical intervention studies evaluating the effects of pharmacological and bioactive interventions on serum OVA-specific IgE levels and nasal symptoms in OVA-induced AR animal models. The pooled results demonstrated that these interventions significantly reduced serum OVA-specific IgE (SMD = −3.03), nasal rubbing (SMD = −5.24), and nasal sneezing (SMD = −4.29) relative to vehicle or untreated controls. These large effect sizes were consistent across all three outcomes and remained robust in leave-one-out sensitivity analyses, indicating that no single comparison disproportionately altered the direction or statistical significance of the pooled estimates. Substantial statistical heterogeneity (I^2 > 75%) was observed across all outcomes,

which was anticipated given the diversity of interventions, dosing regimens, animal strains, and measurement protocols among the included studies.

The present findings are consistent with the broader preclinical literature supporting the anti-allergic potential of natural products and bioactive compounds in IgE-mediated diseases. Previous narrative reviews have highlighted the immunomodulatory properties of flavonoids, terpenoids, and polyphenolic compounds in AR models, but quantitative estimates of pooled effect sizes have been lacking (Mlcek et al., 2016; Tanaka & Takahashi, 2013). Individual compounds identified in this review — including curcumin, apigenin, and wogonin — have been separately reported to suppress Th2-mediated cytokine production and IgE synthesis in both in vitro and in vivo settings (Chung et al., 2012; Guo et al., 2015; Park et al., 2008). The subgroup analyses revealed a statistically significant difference between AR model types for nasal sneezing under both common-effect and random-effects models, while the differences for IgE and nasal rubbing were significant only under the common-effect model. These findings suggest that model-specific methodological variations may contribute to observed heterogeneity, although the limited number of studies within certain subgroups precludes definitive conclusions.

The mechanistic basis for the observed treatment effects likely involves modulation of the Th2-polarised immune response at multiple levels. OVA sensitisation induces antigen-specific IgE production through a cascade initiated by dendritic cell antigen presentation to naïve $CD4^+$ T cells, with subsequent Th2 differentiation and IL-4-dependent B-cell class switching to IgE (Holgate & Polosa, 2008). Several of the compounds evaluated in the included studies have been shown to inhibit nuclear factor kappa B (NF-κB) signalling, suppress Th2 cytokine gene transcription, reduce mast cell degranulation, and attenuate eosinophilic infiltration into the nasal mucosa (Lawrence, 2009; Galli et al., 2005; Rothenberg & Hogan, 2006). The reduction in OVA-specific IgE observed in the meta-analysis likely reflects upstream suppression of Th2 cytokines, while the improvements in nasal rubbing and sneezing scores correspond to downstream attenuation of effector mechanisms including histamine release, leukotriene synthesis, and neurogenic inflammation. The convergence of significant effects across immunological (IgE) and behavioural (nasal symptoms) endpoints strengthens the biological plausibility of the overall findings.

The translational implications of these findings should be considered within the inherent constraints of preclinical evidence. While OVA-induced AR models recapitulate key immunological and symptomatic features of human AR, notable differences in nasal anatomy, immune system complexity, allergen exposure patterns, and pharmacokinetics between rodents and humans limit direct clinical extrapolation (Zosky & Sly, 2007). The exclusive use of OVA as the sensitising allergen does not capture the full spectrum of clinically relevant aeroallergens, and the acute to subacute nature of most rodent models may not reflect chronic AR phenotypes. Nevertheless, the consistent and large-magnitude effects observed across diverse pharmacological agents provide a strong rationale for advancing the most promising candidates into dose-finding and pharmacokinetic studies, and ultimately into human clinical trials. The identification of compounds with pleiotropic anti-inflammatory and immunomodulatory properties may be particularly relevant for patients with inadequate responses to conventional AR therapies.

Several limitations of this review merit acknowledgement. First, the majority of SYRCLE domains were rated as unclear risk of bias due to insufficient methodological reporting, which is a pervasive limitation in preclinical animal research. The absence of reported randomisation, allocation concealment, and blinding introduces the possibility of selection, performance, and detection biases that may inflate treatment effect estimates. Second, substantial heterogeneity was observed across all outcomes, likely attributable to variability in compound classes, doses, administration routes, animal strains, and outcome

measurement techniques. Although subgroup and sensitivity analyses were conducted, the limited number of studies within certain subgroups constrained the statistical power of these secondary analyses. Third, publication bias was not formally assessed due to the small number of included studies per outcome, which renders funnel plot-based methods unreliable. Fourth, several values were extracted from graphical presentations, introducing a degree of measurement imprecision; additionally, Li (2018) did not clearly report the number of animals per group and was therefore treated cautiously in interpretation. Fifth, although no language restrictions were applied at the search stage, the search was limited to PubMed, EMBASE, and Scopus and may have missed relevant non-indexed or regional studies. Despite these limitations, the consistency of findings across outcomes and the robustness of sensitivity analyses support the overall validity of the conclusions.

CONCLUSION

This systematic review and meta-analysis provides the first comprehensive quantitative synthesis of pharmacological and bioactive treatment effects on serum OVA-specific IgE and nasal symptom scores in OVA-induced AR animal models. The evidence demonstrates that these interventions consistently and significantly attenuated both immunological and behavioral markers of allergic rhinitis across a diverse array of compounds. These preclinical findings support the continued investigation of natural products, bioactive agents, and related pharmacological candidates as potential therapies for allergic rhinitis and provide a quantitative foundation for prioritizing the most promising agents for translational development. Future studies should prioritize improved methodological rigor, standardized outcome reporting, and the evaluation of compound-specific dose-response relationships to strengthen the evidence base for clinical translation.

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