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Rhizoma Atractylodis Macrocephalae (Atractylodes Macrocephala Koidz.) ameliorates asthma via inhibiting TNF-α

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Abstract

Objective. The aim of thev study is to investigate the therapeutic effects and underlying mechanisms of RAM in a house dust mite (HDM)-induced murine model of allergic asthma, with a focus on necroptosis and TNF signaling.

Materials and Method. Allergic asthma was induced in mice and HBE cells by HDM challenge. Animals were treated with RAM to assess its effects on airway inflammation, hyperresponsiveness, IgE production, and cytokine/chemokine expression. *In vitro,* necroptosis markers (RIPK1, RIPK3, p-MLKL), inflammatory cytokines, and cell viability were evaluated in HBE cells. Network pharmacology and molecular docking were employed to predict RAM's bioactive compounds and their primary targets, with a focus on the necroptosis pathway. The role of TNF was further validated through overexpression experiments in HBE cells.

Results. RAM treatment significantly alleviated asthma phenotypes, reducing inflammatory cell infiltration in BALF, serum IgE levels, airway hyperresponsiveness, and pulmonary expression of Cxcl1/Cxcl2. RAM suppressed expression of Ripk1, Ripk3, p-MLKL, and caspase-3, alongside reduced proinflammatory cytokines (IL-1α, IL-1β, IL-33), in HDM-induced mice and HBE cells. Network pharmacology identified TNF as a top-ranked target within the necroptosis pathway, and molecular docking confirmed binding affinities between TNF and five RAM compounds. Experimentally, RAM downregulated TNF expression in mouse lungs and HBE cells. TNF overexpression reversed RAM's protective effects, restoring Ripk1/Ripk3 expression and diminishing cell viability.

Conclusions. RAM may attenuate allergic asthma by inhibiting the TNF-mediated necroptosis pathway. This study provides a pharmacological basis for RAM as a promising therapeutic agent for asthma treatment.

Key words

TNF, asthma, herb, necroptosis, network pharmacology

INTRODUCTION

Asthma remains a major challenge to global health, affecting hundreds of millions of people and imposing a substantial socio-economic burden, particularly in regions where prevalence continues to grow [1, 2]. Although overall rates have plateaued in some high-income countries, they are rising persistently across many low- and middle-income regions [3]. In China, a large-scale epidemiological study indicated that adult asthma affects over 45 million individuals, underscoring its significant impact on public health [4, 5]. Pathologically, asthma is characterized by chronic airway inflammation, bronchial hyperresponsiveness, and structural remodeling [6]. The disease is increasingly recognized for its heterogeneity, encompassing various endotypes and phenotypes driven by distinct immune mechanisms [7]. Allergic asthma constitutes a predominant phenotype, encountered in approximately 90% of paediatric cases and up to 50% in adults [8]. Both adaptive and innate immunity play critical and interconnected roles in the pathogenesis of allergic asthma [1]. Emerging evidence highlights the importance of regulated cell death pathways, particularly necroptosis, in shaping airway inflammation and immune responses in asthma [9]. Necroptosis is a pro-inflammatory form of programmed cell death mediated by Ripk1, Ripk3, and MLKL, leading to plasma membrane rupture and release of damage-associated molecular patterns [10]. It has been reported that necroptosis of airway epithelial cells contributes to the exacerbation of allergic airway inflammation following HDM sensitization and challenge [11]. Current therapeutic strategies primarily focus on symptom control and suppression of allergic inflammation [8, 12]. The role of necroptosis in exacerbating inflammation and promoting disease chronicity offers a new perspective for therapeutic intervention.

Owing to its recognized therapeutic benefits and favourable safety profile, Traditional Chinese Medicine (TCM) has been increasingly integrated into standard management strategies for asthma in China [13–15]. Clinical evidence suggests that, compared to conventional medicine, traditional Chinese herbal therapy may offer superior efficacy in treating paediatric asthma, as measured by the total effective rate [13]. In recent years, the cellular and molecular mechanisms through which herbs exert their therapeutic effects on asthma have become a major focus of experimental research. For example, the pair of herbs *Ephedra sinica Stapf* and *Schisandra chinensis* (Turcz.) Baill can attenuate allergic airway inflammation and remodeling in allergic asthma,

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primarily via targeting and inhibiting the PLC/TRPC1/PI3K/AKT/NF-κB axis [16]. *Adenophora stricta* Miq. root can relieve allergic asthma through targeting and inhibiting the same axis. [17]. Glycyrrhizae uralensis can affect the expression of T-bet and GATA-3 genes in children with allergic asthma [18]. Rhizoma Atractylodis Macrocephalae (RAM) (the rhizome of *Atractylodes Macrocephala* Koidz.) is contained in an antiasthmatic TCM formula Yupingfeng San [19]. It can reduce IL-6, IFN-γ, and TNF-α levels and enhance immune function in naturally aging rats [20]. However, the potential mechanism underlying its effectiveness against asthma remains elusive.

The study assesses the collaborative anti-asthma effect of RAM in an asthma mouse model. Network pharmacology and *in vitro* analysis were performed to reveal the potential mechanisms of RAM for anti-asthma in terms of necroptosis.

MATERIALS AND METHOD

Preparation of RAM extract. The crude herbal material of RAM (Kanglun Chinese Herbal Medicine Drinks Slice Co., Ltd., Zhejiang, China) was pulverized into powder. Extraction was performed using 100 mL of aqueous ethanol at varying concentrations under heating reflux at 100 °C for 2 hours. The resulting extract was filtered and concentrated by vacuum evaporation. The quality control on TAM herb, including definition of the correct plants and origin of production,was confirmed according to the guidelines defined by Chinese State Food and Drug Administration (SFDA). The residual solution was subsequently lyophilized to obtain a dried powder, with a yield of 21.52%. The chemical components for TAM extracts were detected by UPLC-MS for quality control.The lyophilized extract was stored at -20 and used within 2 weeks. Based on this yield, the appropriate daily dose of RAM herb for a 70-kg adult (minimum 6 g and maximum 12 g) was converted to the mouse-equivalent dose using the body surface area normalization method, resulting in a daily administration of 72 mg (low RAM) and 145 mg (high RAM). The lyophilized extract powder of RAM was prepared in the same batch for animal administration and cell culture to ensure consistent quality.

Mouse models of allergic asthma and treatment. C57BL/6J mice (8 weeks old) were sourced from Hangzhou Medical College (License No. SYXK (zhe) 2024–0010). Animals were housed under controlled temperature and humidity conditions with a standard light–dark cycle, and provided *ad libitum* access to rodent diet and water. All experimental procedures were approved by the Institutional Animal Care and Use Committee of Tongde Hospital of Zhejiang Province. The mice were allocated to experimental groups at random, utilizing a computer-generated sequence of random numbers to guarantee impartial distribution.

To establish the allergic asthma model, mice were intranasally challenged with HDM (Dermatophagoides pteronyssinus, extract XPB91D3A25; Greer Laboratories, USA) daily on days 1–5 and 8–12, for a total of 10 challenges [21]. Control mice received equal volumes of saline following the same schedule. Mice in the AA+Low RAM and AA+High RAM groups were orally administered RAM extract 30 minutes prior to each HDM challenge, whereas the control and AA groups received an equivalent volume of normal saline. To eliminate any potential bias, the subsequent assessments were conducted in a blinded manner by evaluators who remained unaware of the outcomes, as well as the groups to which the mice were assigned.

Assessment of airway function. Following anaesthesia, mice were tracheotomized and intubated with an 18-gauge cannula connected to the FlexiVent Pulmonary System (Beijing GYD Labtech., Ltd., China). Paralysis was induced via intraperitoneal injection of decamethonium bromide (0.5 mg), and mechanical ventilation was initiated. Airway hyperresponsiveness was assessed in response to escalating concentrations of nebulized acetylcholine (0–100 mg/ml). Total respiratory system resistance was recorded and expressed in $cmH_2O{\cdot}s/mL$.

Enzyme-linked immunosorbent assay (ELISA). Blood samples were drawn from mice. Plasma and serum were separated, respectively, and stored at -80 °C. Plasma IgE was measured by ELISA using Abcam's IgE Mouse ELISA kit (ab157718; Cambridge, USA). Serum IL1α, IL1β, and IL33 were detected using Abcam's IL-1 alpha Mouse ELISA kit (ab113344), Mouse IL-1 beta ELISA Kit (ab100705), and Mouse IL-33 ELISA Kit (ab213475). All measurements were performed according to the manufacturer's instructions.

Analysis of bronchoalveolar lavage fluid (BALF). At the end of the treatment, BALF was collected by performing 3 sequential instillations and aspirations of 1 mL PBS. The lavage fluid was centrifuged, and the resulting cell pellet was resuspended in PBS. Total cell counts were determined using a TC20 automated cell counter (Bio-Rad Inc., Hercules, USA). Cell culture, transfection, and modeling. HBE cells, a human bronchial epithelial line sourced from Fuheng Biology (Shanghai, China), were cultured in KM medium supplemented with 1% KGS. For transfection, cells were elaborated using EndoFectin™ Max Transfection Reagent (Genecopoeia, China) with either a control vector (pcDNA nc) or a plasmid encoding TNF (pcDNA TNF) for 24 hours, according to the manufacturer's instructions. To establish an *in vitro* asthma model, HBE cells were stimulated with 100 μg/mL HDM for 24 hours. Control cells were treated with an equal volume of PBS.

Real-time reverse-transcription PCR (RT-qPCR). Total RNA was extracted from cells or mouse lung tissues using the MolPure® Cell/Tissue Total RNA Kit (Yeasen Biotechnology, Shanghai, China). Subsequently, cDNA synthesis was carried out with Superscript Reverse Transcriptase (Invitrogen, USA). Quantitative PCR was performed using a reaction mixture containing cDNA, gene-specific primers, and SYBR Green PCR master mix (Qiagen, Hilden, Germany). Relative expression levels were normalized to the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (Gapdh).

Network pharmacology analyses of RAM. The active pharmaceutical chemical constituents of RAM were collected from the TCMSP (OB ≥ 30%, DL ≥ 0.18), TCMSuite, and HIT 2.0 databases. The targets were also obtained from these databases and normalized using the Uniprot protein database. Disease genes associated with allergic asthma were retrieved from the Genecards, Drugbank, and OMIM databases using the key words 'Allergic Asthma'. Entries

from Genecards were retained only if their relevance score exceeded 5 times the mean score. All candidate genes from the Drugbank and OMIM databases were included without further filtering. The resulting gene sets from all 3 databases were merged, and duplicate entries were eliminated to yield a non-redundant list of allergic asthma-related targets. The intersection between these targets and those related to RAM was identified using the 'VennDiagram' package in R, resulting in a set of common target genes. A triple network illustrating the relationships among RAM, active components, and allergic asthma was constructed and visualized using Cytoscape 3.7.2.

Molecular docking. The 3-dimensional structures of chemical compounds were acquired from the PubChem database. The crystal structure of TNF protein was obtained from the Protein Data Bank (PDB). Pre-processing of the protein and ligands was carried out using Yinfotek cloud-based tools. Molecular docking simulations were performed using the CB-Dock2 server with AutoDock Vina to evaluate the binding of the compounds to predicted binding pockets on the target protein.

Western blot analysis. Snap-frozen lung tissue samples were homogenized in ice-cold Enhanced RIPA Lysis Buffer (Applygen, Beijing, China). The total protein concentration was quantified using a BCA assay. Equivalent amounts of protein were separated by SDS-PAGE and electrophoretically transferred to PVDF membranes using a Pierce G2 Fast Blotter system (Thermo Scientific, Waltham, USA). Following blocking, the membranes were probed with primary antibodies against p-MLKL, and then incubated with corresponding HRP-conjugated secondary antibodies. Specific protein bands were detected using a chemiluminescent substrate (Pierce) and captured with a chemiluminescence imaging system.

Cell viability assay and determination of IC50 to RAM. Cell viability and the half-maximal inhibitory concentration (IC50) of RAM were assessed using the Cell Counting Kit-8 (CCK8, Sigma, St. Louis, USA). Cells were plated in 96-well plates at a density of 5×10^3 cells per well. To determine IC50, cells were treated with RAM at final concentrations of 0, 2.5, 5, 10, 20, 40, and 80 mg/mL. For cell viability assessment, a concentration of 2 mg/mL RAM was applied. Following a 48-hour incubation period, CCK8 reagent was added according to the manufacturer's instructions to quantify cell viability. All experiments were conducted in triplicate.

Statistical analyses. For animal experiments, the biological replicates from 5 mice were used for experiments with 3 technical replicates. For cell experiments, statistical analysis of data was performed on 4 independent experiments per cell line. All data are presented as means±standard deviation. Statistical analyses were conducted using GraphPad Prism version 8.0. Data were analyzed by unpaired t-test, one-way or two-way ANOVA, followed by Tukey's multiple comparisons test. Significance level was denoted as $P < 0.05$.

RESULTS

RAM treatment alleviated asthma in HDM-challenged mice. To investigate the role of RAM in allergic asthma, mice were challenged using HDM. In HDM-challenged mice, total cells were significantly increased in BALF compared with control group, which was reversed by low dose and high dose of RAM treatment (Fig. 1A). It was also found that plasma immunoglobulin E was increased in the asthma model, but RAM treatment combatted this increase (Fig. 1B). Airway resistance, an indicator of airway hyperresponsiveness, was significantly decreased after RAM treatment in HDM-challenged mice (Fig. 1C). Elevations in the levels of several cytokines and chemokines, including CXCL1 and CXCL2 was seen to be elevated in the lungs following repeated HDM challenge [22]. While HDM challenge increased the mRNA levels of CXCL1 and CXCL2, RAM treatment prevented these increases (Fig. 1D).

RAM ameliorated HDM-induced necroptosis and inflammation. RT-PCR analysis showed that HDM challenge upregulated Ripk1 and Ripk3 mRNA levels in the mouse lungs; however, these mRNAs were markedly reduced in after RAM treatment (Fig. 2A). Similarly, quantitative analysis revealed significantly higher protein levels of p-MLKL in HDM-challenged mice than the controls, which was reduced by RAM treatment (Fig. 2B). Concurrently, the elevation of lung proinflammatory cytokines (IL-1α, IL-1β, and IL-33) associated with asthma was suppressed by RAM treatment (Fig. 2C). To explore the non-cytotoxic concentration of RAM, HBE cells were treated with different concentrations of RAM, and a IC10 of 1.87 mg/mL was obtained (Fig. 2D). For *in vitro* model, HBE cells were exposed to HDM, and a decrease in cell viability was observed; whereas RAM treatment recovered the cell viability (Fig. 2E). As expected, LPS induced the expression of Ripk1 mRNA and Ripk3 mRNA in HBE, indicating the activation of necroptosis; however, the expression of Ripk1 and Ripk3 in HBE induced by HDM decreased after RAM treatment (Fig. 2F).

RAM treated asthma in a multi-target and multi-pathway manner. Network pharmacology analysis identified 31 active compounds in RAM targeting 556 genes (Supplementary Fig. 1). Among these targets, 38 were associated with allergic asthma (Fig. 3A). A compound-target-disease network was constructed, comprising 19 RAM chemicals and 40 asthma-related genes (Fig. 3B). KEGG pathway enrichment analysis further revealed that 7 key targets – TNF, IFNG, IL1A, IL1B, IL33, TLR4, and TNFSF10 were significantly enriched in the necroptosis pathway (Fig. 3C). In the network, TNF ranked first at the level of degree among the targets.

Molecular docking results of TNF with corresponding chemical components. Next, molecular docking was performed. The representative molecular docking of TNF with Alpha-Humulone (Fig. 4A), Atractylenolide I (Fig. 4B), Luteolin (Fig. 4C), Udp-glucuronic acid (Fig. 4D), and (-)-Epicatechin (Fig. 4E), respectively, supported the potential mechanism of RAM via moderating TNF.

RAM inhibited TNF in asthma. The expression levels of TNF in the lung tissues of mice and HBE cells were then measured. RT-qPCR showed that RAM reduced the mRNA

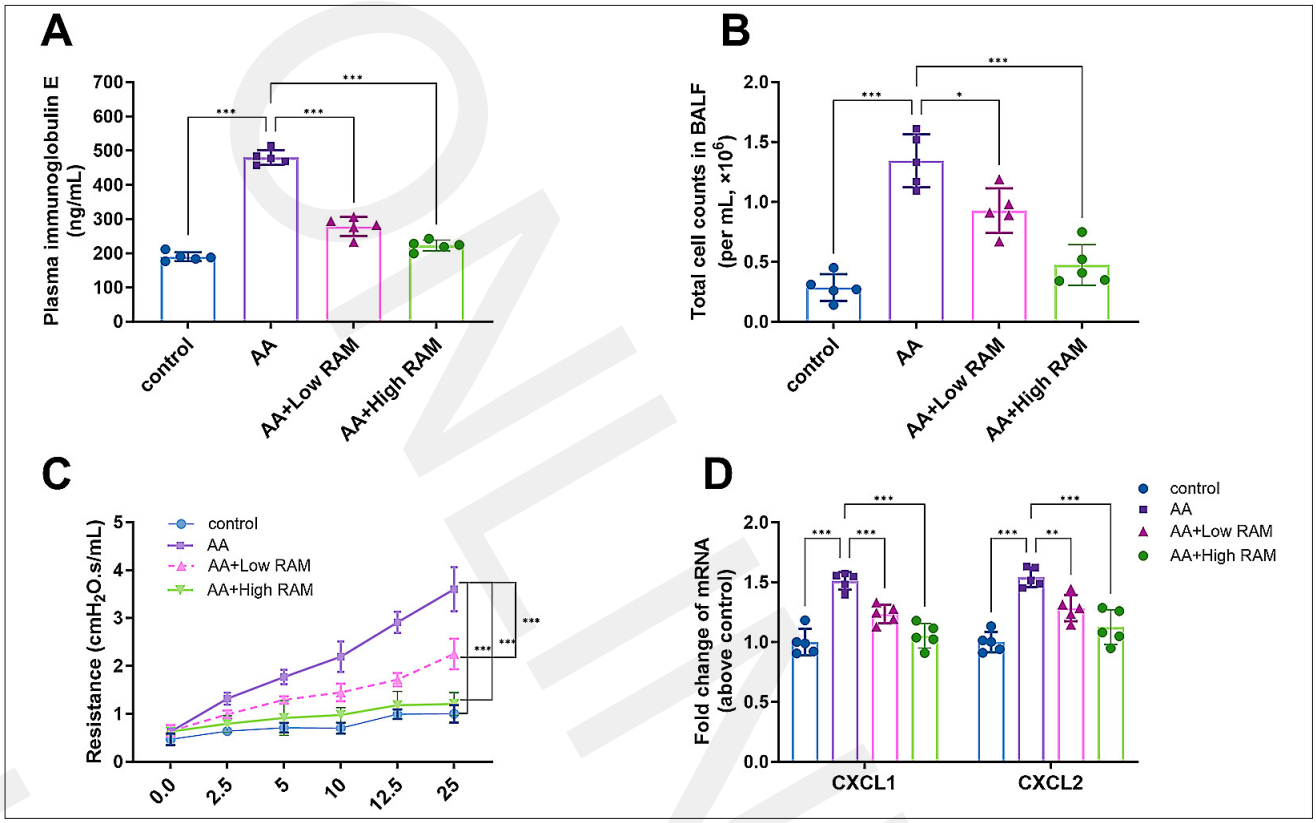


Figure 1. Rhizoma Atractylodis Macrocephalae (RAM) treatment ameliorated allergic asthma in mice. (A) RAM reduced plasma immunoglobulin E levels, as measured by ELISA. (B) Total inflammatory cell counts in bronchoalveolar lavage fluid (BALF) were decreased by RAM. (C) Airway hyperresponsiveness, assessed in response to methacholine challenge, was attenuated by RAM. (D) RAM inhibited the expression of CXCL1 and CXCL2 mRNA in lung tissue.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

expression levels of TNF in the lung tissues of mice with allergic asthma (Fig. 5A) and HDM-exposed HBE cells (Fig. 5B). After transfection with TNF pcDNA, TNF mRNA level was increased in RAM-treated HBE cells (Fig. 5C). TNF overexpression increased the levels of Ripk1 (Fig. 5D) and Ripk3 (Fig. 5E) in RAM-treated HBE cells. CCK8 assays revealed a notable reduction in HBE cell viability even under RAM treatment (Fig. 5F).

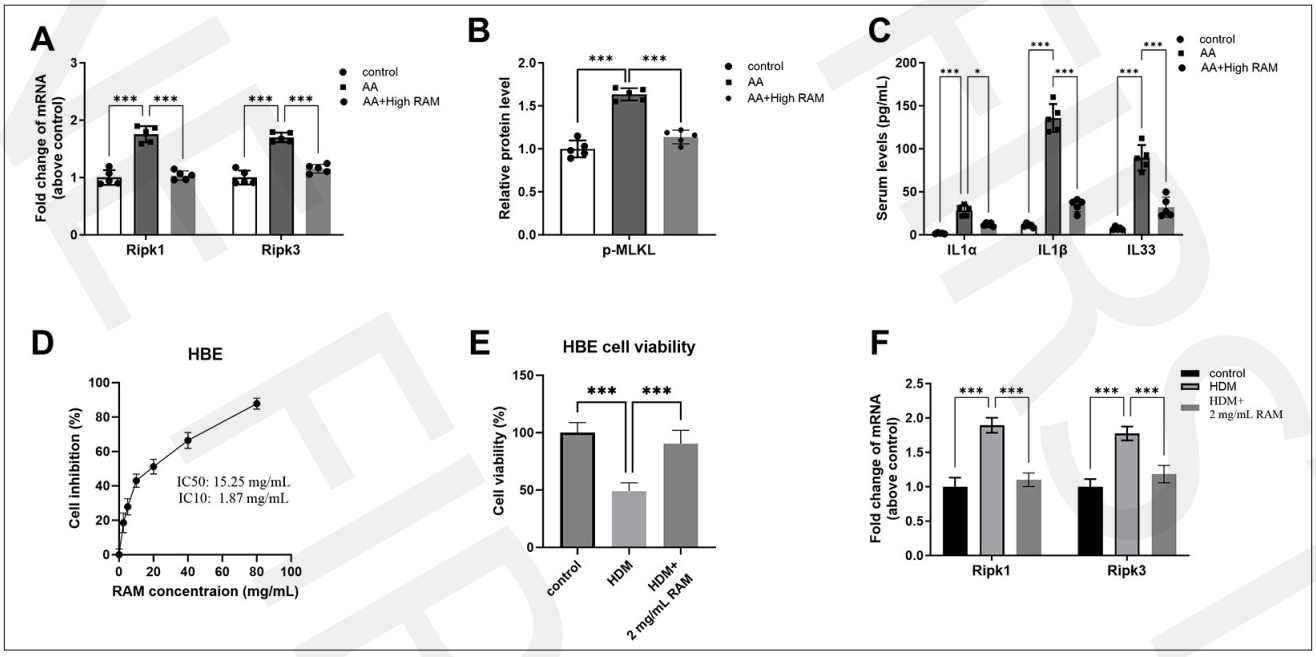


Figure 2. Rhizoma Atractylodis Macrocephalae (RAM) treatment ameliorated necroptosis in asthma. (A) Ripk1 and Ripk3 mRNAs in lung tissue were assessed by RT-qPCR. (B) Western blot analysis of p-MLKL. (C) Serum levels of IL1α, IL-1β, and IL33. (D) Inhibition of cell viability by different concentrations of RAM. (E) Cell viability of HDM-exposed HBE cells under RAM treatment. (F) Ripk1 and Ripk3 mRNAs in HBE cells were assessed by RT-qPCR.
*$P < 0.05$, ***$P < 0.001$

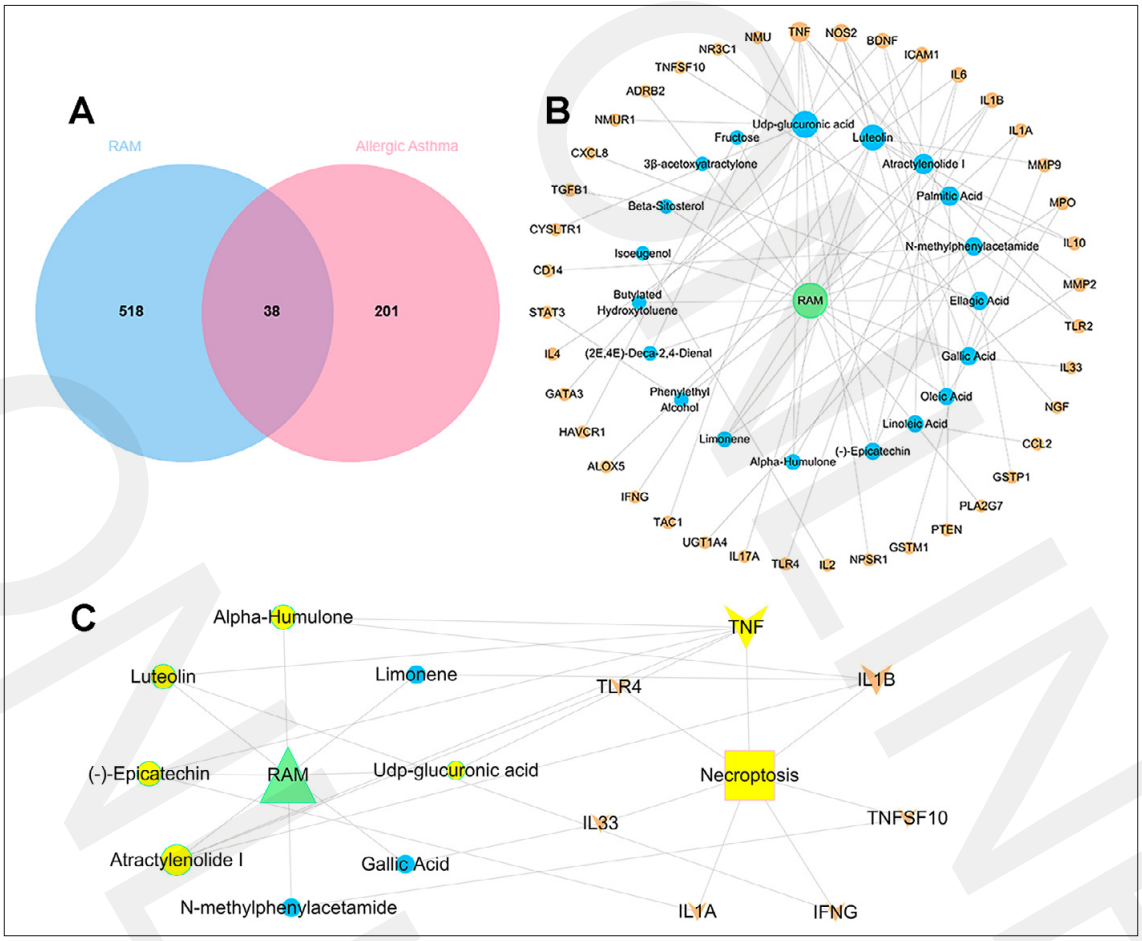


Figure 3. Network pharmacology analysis of Rhizoma Atractylodis Macrocephalae (RAM). (A) VENN diagram of common genes between RAM targets and allergic asthma-associated genes. (B) The RAM-chemical-target network. (C) Network of RAM-chemical-target-necroptosis pathway

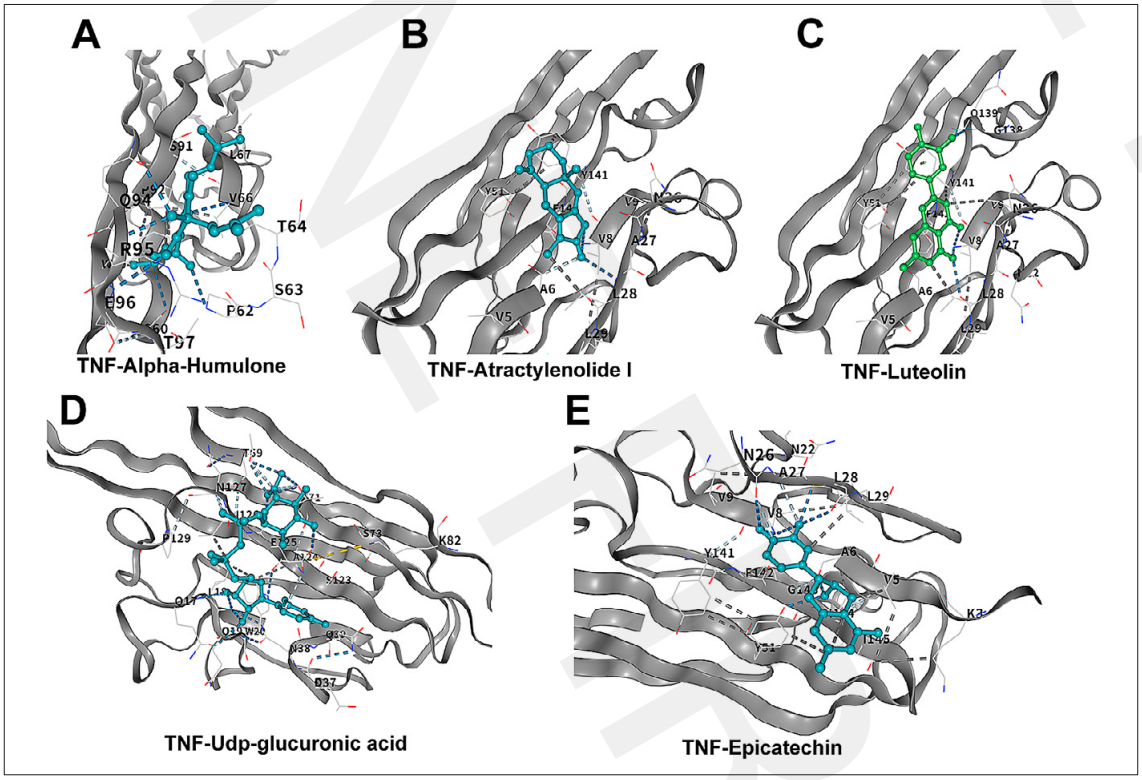


Figure 4. Molecular docking images for TNF with Alpha-Humulone (A), Atractylenolide I (B), Luteolin (C), Udp-glucuronic acid (D), and (-)-Epicatechin (E).

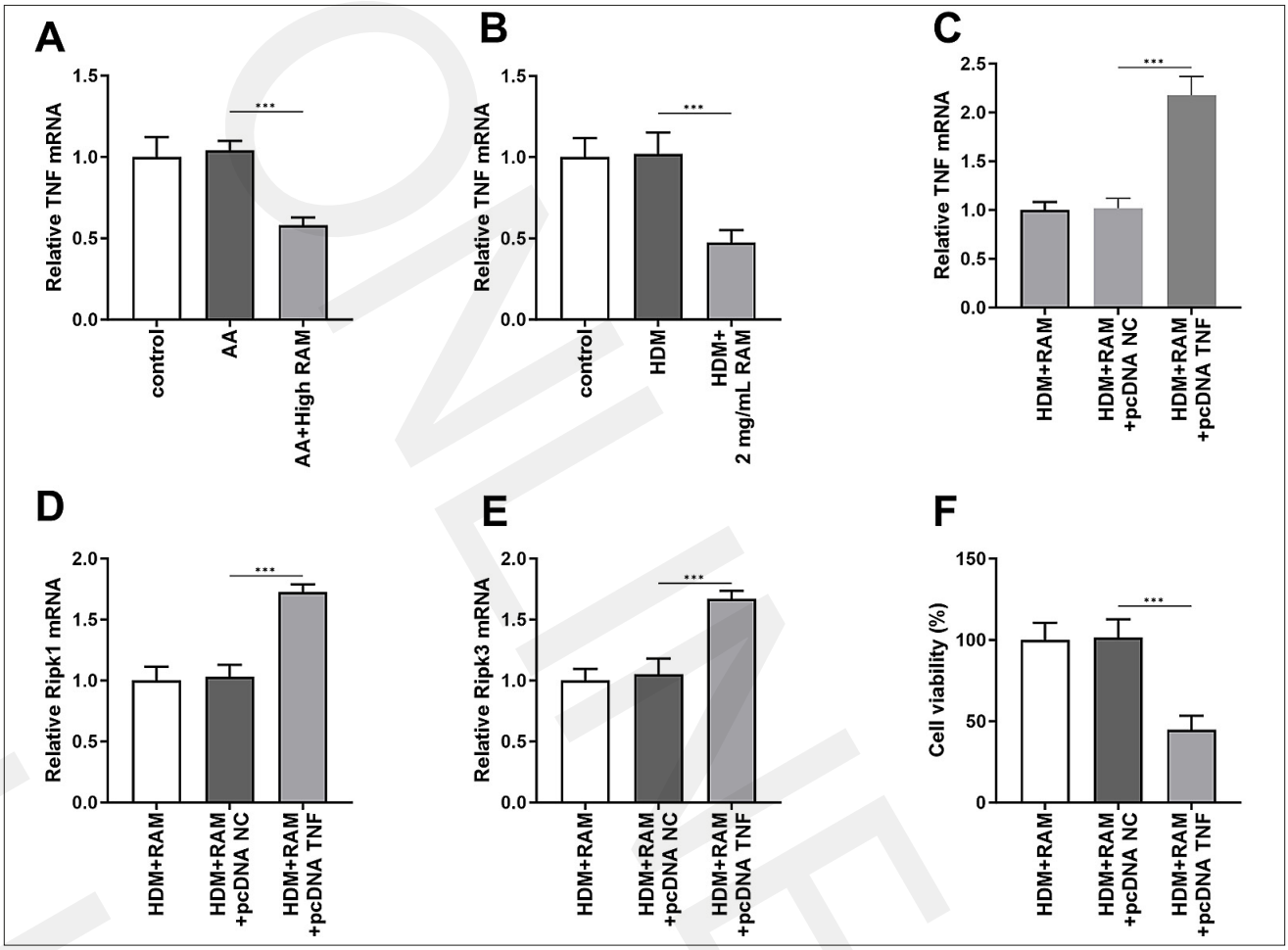


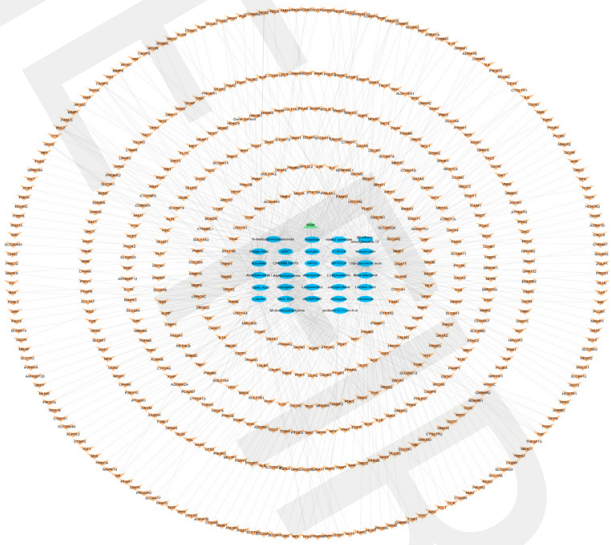
Figure 5. Rhizoma Atractylodis Macrocephalae (RAM) ameliorated asthma via TNF. (A) TNF mRNAs in lung tissue. (B) TNF mRNAs in HBE cells under RAM treatment. (C) TNF mRNAs in transfected HBE cells. (D) Ripk1 mRNA in transfected HBE cells. (E) Ripk3 mRNA in transfected HBE cells. (F) Cell viability of transfected HBE cells. ***$P < 0.001$

DISCUSSION

Due to their multi-component nature and historical use in traditional medicine, herbal medicines have garnered increasing attention as potential therapeutic agents for asthma [14]. Recent studies have highlighted their ability to modulate immune responses and attenuate airway inflammation [23, 24]. The present study demonstrates that RAM can alleviate hallmark features of allergic asthma in an HDM-induced murine model. RAM treatment reduced inflammatory cell infiltration in bronchoalveolar lavage fluid, decreased IgE levels, improved airway hyperresponsiveness, and suppressed the expression of key chemokines such as CXCL1 and CXCL2. These findings suggest that RAM possesses anti-inflammatory and immunomodulatory properties, supporting its potential as a multi-target therapeutic agent for asthma management.

In models of inflammation, such as asthma, various forms of regulated cell death frequently manifest: certain cells experience apoptosis while others undergo necroptosis; inflammatory responses and cellular stress may trigger secondary caspase activation; and numerous death pathways can be activated concurrently [9, 25]. Necroptosis, a programmed form of necrotic cell death mediated by Ripk1, Ripk3, and MLKL, has recently been implicated in the pathogenesis of asthma, contributing to airway inflammation and tissue damage [26]. Evidence from a murine model reveals that HDM-induced allergic inflammation exacerbates asthma through airway epithelial cell necroptosis [12].

The results obtained in the current study indicate that



Supplementary Figure 1. The network containing chemicals and the corresponding targets for Rhizoma Atractylodis Macrocephalae (RAM)

HDM challenge induces necroptotic activity in mouse lungs, as evidenced by elevated mRNA levels of Ripk1 and Ripk3 and increased phosphorylation of MLKL. Remarkably, RAM treatment significantly suppressed these markers, indicating its inhibitory effect on necroptosis. Furthermore, RAM reduced the expression of proinflammatory cytokines IL-1α, IL-1β, and IL-33, which are associated with necroptosis-mediated inflammation. *In vitro* experiments confirmed that RAM restored cell viability in HDM-exposed HBE cells and downregulated the expression of necroptosis-related markers. These results collectively suggest that the anti-asthmatic effects of RAM may be partly attributable to the suppression of necroptotic pathways.

Tumour necrosis factor (TNF) is a pivotal cytokine in asthma pathogenesis, known to drive inflammatory responses, enhance airway hyperreactivity, and promote immune cell recruitment [9, 27]. Importantly, TNF can initiate necroptosis through activation of the Ripk1/Ripk3/MLKL axis, forming a vicious cycle that exacerbates inflammation [28]. Network pharmacology analysis by the authors identified TNF as a central target of RAM, which was further validated experimentally. RAM administration downregulated TNF expression both in murine lung tissues and in HDM-stimulated HBE cells. Conversely, overexpression of TNF in RAM-treated HBE cells reversed the protective effects, leading to increased expression of Ripk1 and Ripk3 and reduced cell viability. This indicates that TNF is a critical target through which RAM modulates necroptosis and ameliorates asthma phenotypes.

CONCLUSION

The study demonstrates that RAM confers protection against HDM-induced allergic asthma. Such an effect is likely mediated through a multi-target strategy, with the TNF and necroptosis being implicated.

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