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## Extract of *Brassica rapa* suppresses ovalbumin-induced asthma by down-regulating NF- $\kappa$ B and p38 MAPK activity

Yun-Lei Dai<sup>1</sup>, Gui-Lian Shao<sup>2</sup> and Fang Wang<sup>3</sup>

<sup>1</sup>Department of Pediatrics, The First Affiliated Hospital of Henan University of TCM, Zhengzhou 450 000, China;

<sup>2</sup>Department of Pediatrics, Weihai Meternal and Child Health Hospital, Weihai 264 200, China; <sup>3</sup>Department of Pediatrics, Zhengzhou Central Hospital Affiliated to Zhengzhou University, Zhengzhou 450 007, China.

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### Abstract

Asthma is one of the most common chronic inflammatory diseases characterized by airway infiltration of inflammatory cells inducing hyperresponsiveness. Due to the inefficacy of currently used drugs to definitely cure asthma, there is an insistent need for identification of novel therapies. In the present research, efficiency of *Brassica rapa* extract in asthma induced mouse model was investigated. Asthma was induced in mice by ovalbumin induction. The extract (125-500 mg/kg) effectively reduced ovalbumin-specific IgE in serum and levels of interleukins (IL): IL-4, IL-5 and IL-13 in bronchoalveolar lavage fluid (BALF). *B. rapa* extract inhibited inflammatory cell infiltration in BALF and also improved lung compliance and airway resistance. The extract caused marked reduction in the expression levels of phosphorylated ERK, p38, I $\kappa$ B- $\alpha$  and NF- $\kappa$ B, however dose-dependent activation of JNK was observed. The extract of *B. rapa*, thus, was effective in suppressing ovalbumin-induced asthma.

### Introduction

Asthma is one of the most common chronic inflammatory diseases, characterized by lung eosinophilia, mucus hypersecretion, and airway hyperresponsiveness (AHR) (Elias et al., 2003; Janson, 2010). The incidence of asthma is increasing at an alarming rate. It is estimated that about 300 million people suffer from asthma, and 250,000 asthma-related deaths occur each year.

Asthma progression is associated with the expression of a broad array of inflammatory proteins. Studies have demonstrated that many of these responses are contributed by T-helper2 (Th2) cells (Busse and Lemanske, 2001; Herrick and Bottomly, 2003). IL-4, IL-5 and IL-13 cytokines secreted from Th2 cells are crucial in allergic airway inflammation (Leigh et al., 2004). NF- $\kappa$ B is also involved in the production of Th2 cytokines and in the recruitment of inflammatory cells (Choi et al., 2004; Kang et al., 2009). Mitogen-activated protein (MAP) p38

kinase has been reported in the activation of various immune cells (Griswold and Young, 1996; Chang and Karin, 2001). Thus, inhibitors of these inflammatory mediators could be considered as anti-inflammatory drug candidates in asthma (Chio and Park, 2012).

Currently, corticosteroids are considered to be most effective for reducing the symptoms of asthma; however, they do not cure or alter the progression of the disease and also have been reported of systemic and local adverse effects (Walsh, 2005; Shahzad et al., 2009; Hocaoglu et al., 2011). The chronic nature of asthma and inefficacy of the currently used drugs has caused to explore for new therapies (Li, 2009). Complementary or alternative medicine (CAM) approaches are being increasingly used (Li and Brown, 2009). *Brassicaceae* vegetables consumed widely have beneficial effects due to their bioactive compounds with antioxidant capacity, as vitamins (Wu et al., 2004), phenolics and flavonoids (Powers et al., 2004; Podsedek, 2007). In the present study, the efficacy of Brassica vegetable, *Brassica rapa*



*chinensis* on ovalbumin-induced asthma was investigated.

## Materials and Methods

### Reagents and antibodies

The IL-4, IL-5 and IL-13 ELISA kits were purchased from BioLegend, Inc. Camino Santa Fe, Suite E San Diego, CA, USA. All the antibodies used in the study were procured from Cell Signaling Technology Inc, Beverly, MA, USA. Ovalbumin (OVA) was obtained from Sigma-Aldrich, St. Louis MO, USA. All other chemicals and reagents were purchased from Sigma-Aldrich, St. Louis MO, USA unless otherwise are mentioned.

### Preparation of *B. rapa* extract (BRCE)

*B. rapa* was purchased from local grocery mart and were shade dried and finely powdered. A quantity of 100 g of the fine powder was extracted with boiling water for 4 hours and filtered. The residue was extracted again and the supernatants were pooled, condensed and lyophilised for storage at -4°C until use.

### Animals

Female BALB/c mice (18-20 g) were obtained from the Centre of Experimental Animals of Baiqiu Medical College of Jilin University (Jilin, China). All animals were housed in a room under controlled environment (25 ± 1°C, 40-60% humidity) and supplied with water and food provided *ad libitum*. The mice were acclimatized to in house conditions for a week prior experimentation. All animal experiments were performed in accordance with the guide for the Care and Use of Laboratory Animals published by the US National Institute of Health.

### Ovalbumin sensitization and challenge

Mice (BALB/c) were sensitized with OVA as described by Oh et al. (2002) with some modifications. Briefly, OVA (500 µg/mL) in PBS was mixed with an equal volume of 10% (w/v) aqueous aluminum potassium sulfate (alum) and incubated at room temperature for 1 hour after adjusting the pH to 6.5 with 10 N NaOH. Following centrifugation at 750 g for 5 min, the OVA/alum pellet was resuspended at its original volume in distilled water. The mice received 100 µg OVA (0.2 mL of 500 µg/mL solution in normal saline) intra peritoneally (i.p) complexed with alum on the first day, and were challenged intranasally (i.n.) on days 8, 15, 18, and 21, as described by Oh et al. (2002). Mice were prepared for the challenge by anesthetizing with an i.p injection of 0.2 mL of a mixture of ketamine (0.44 mg/mL) and xylazine (6.3 mg/mL) in normal saline, and were placed on a board in the supine position. Mice received 250 µg OVA (100 µL of a 2.5 mg/mL solution)

on day 8 and on days 15, 18, and 21 and were challenged with 125 µg OVA (50 µL of 2.5 mg/mL solution). The control mice received no OVA injections. The treatment group animals were given *B. rapa* extract (125, 250 and 500 mg/kg b.wt; orally) every day from day 1 to day 21. On the days of OVA administration, the mice received *B. rapa* extract an hour before injections. DEX (2 mg/kg) was injected as i.p as a positive control on the days of OVA injection an hour prior.

### OVA-specific IgE

At 24 hours following the last OVA challenge, blood was collected and centrifuged at 3000 rpm for 10 min at 4°C and the serum was stored at -80°C for measurement of IgE. OVA-specific serum IgE levels were determined by enzyme linked immunosorbent absorbent assay (ELISA). Briefly, microplate wells were coated with 1% OVA in coating buffer (0.05 M sodium carbonate-bicarbonate, pH 9.6) and kept overnight at 4°C. The wells were then incubated with blocking buffer (1% BSA in PBS, pH 7.2) at room temperature for 1 hour and then washed. Diluted serum samples were then added to the microplate, incubated at room temperature for 2 hours, washed and incubated with biotin anti-mouse IgE. This was followed by addition of extravidin-peroxidase at room temperature for 30 min and with 3,3', 5, 5'-tetramethyl-benzidine substrate for 30 min. The enzymatic reaction was stopped using 2 M H<sub>2</sub>SO<sub>4</sub>, and the absorbance was read at 450 nm. Concentrations were determined in duplicates for each sample.

### Analysis of bronchoalveolar lavage fluid (BALF)

The BALF was collected by cannulation in the upper part of the trachea by infusing PBS in three aliquots (0.5, 0.5, 0.5 mL) in a total volume of 1.3 mL. The fluid was centrifuged and the supernatant was stored at -80°C until cytokine assays. The cell pellets were resuspended in PBS for the total cell, eosinophil, and neutrophil counts using hemacytometer by staining with the Wright-Giemsa staining method.

### Assay of cytokines

The BALF as obtained above was centrifuged and the supernatant was used for cytokine assay. The assays were performed according to the manufacturer's instructions. IL-4, IL-5 and IL-13 levels in BALF were measured using specific mouse IL-4, IL-5 and IL-13 ELISA as per manufacturer's instructions.

### Measurements of AHR

AHR was assessed as a change in airway function following challenge with aerosolized methacholine via the airway. The mice were anesthetized after 24 hours of last OVA challenge. Tracheotomy was performed as described by Bao et al. (2007). The internal jugular vein was cannulated and connected to a microsyringe for

intravenous administration of methacholine. Lung compliance (C<sub>dyn</sub>) and airway resistance (RI) in response to increasing concentrations of methacholine were recorded using a whole-body plethysmograph chamber (Buxco, Sharon, CT, USA) as described previously by Teran et al. (1999). The results are expressed as a percentage of the respective basal values in response to PBS.

#### Western blot analysis

Lung tissues of the mice were excised after 24 hours of last OVA challenge. The tissues were homogenized in liquid nitrogen and incubated in lysis buffer with protease and phosphatase inhibitors (Roche, Basel, Switzerland) to obtain extracts of lung protein. The samples were loaded on to 10% SDS-PAGE gels and were transferred to a polyvinylidene difluoride (PVDF) membrane. Following blotting, the blots were exposed to and incubated with specific antibodies against JNK, p38, ERK, p-ERK, p-JNK, p-p38, p-NF- $\kappa$ B p65 and p-I $\kappa$ B in 5% bovine serum albumin (BSA). The membrane was then washed thrice for 5 min each with TBST (Tris-buffered saline and Tween-20). The primary antibody was probed with HRP-conjugated goat anti-rabbit (1:7000) and HRP-conjugated goat anti mouse (1:7000) for 1 hour and washed three times in TBST. Protein bands were visualized using the ECL assay kit (Beyotime, Nantong, China). The band density was normalized to the expression of  $\beta$ -actin.

#### Statistical analysis

Obtained results are represented as mean  $\pm$  SD. Values at  $p < 0.05$  are considered significant as determined by one-way analysis of variance (ANOVA). The values

were analysed using SPSS software (version 17.0).

## Results

Th2-type cytokines play a central role in the pathogenesis of allergic asthma by regulating immunoglobulin E (IgE) production. Markedly ( $p < 0.05$ ) raised levels of serum IgE were found in OVA-induced mice as compared against control mice. *B. rapa* extract at various concentrations (125-500 mg) effectively reduced IgE levels in a dose dependent manner (Figure 1).

BALF collected 24 hours following OVA challenge in OVA-sensitized mice resulted in marked infiltration of inflammatory cells. Significantly increased levels of the total number of cells, neutrophil and eosinophil counts were recorded in BALF of OVA alone induced mice compared to control group (Figure 2A, B and C). However, the inflammatory cell counts in BALF of *B. rapa* extract treated mice were significantly lower as against OVA-challenged mice. *B. rapa* extract at 500 mg dose was more effective in reducing the cell counts when compared to lower doses of 125 and 250 mg, DEX (2 mg/kg) treatment also significantly inhibited the OVA-induced inflammatory infiltration.

Overexpression of Th2-mediated cytokines including IL-4, IL-5, and IL-13 are generally observed in asthma. We used ELISA to determine if *B. rapa* extract (125,250 or 500 mg/kg) treatment could affect cytokine secretion in the BALF. OVA challenge led to significant increases in the levels of IL-4, IL-5 and IL-13 in BALF, compared with control. In *B. rapa* extract treatment, 250 and 500 mg/kg doses were effective in suppressing the levels of

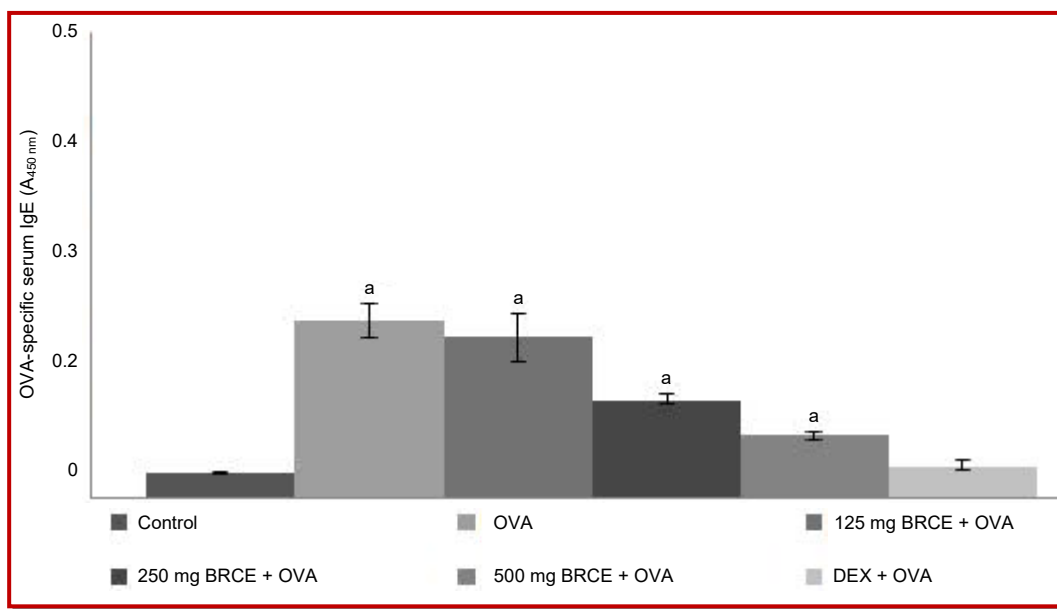


Figure 1: Effect of *Brassica rapa* extract on OVA- specific IgE levels in serum

Values are represented as mean  $\pm$  SD; n=6; <sup>a</sup>represents  $p < 0.05$  compared with control as determined by one-way ANOVA

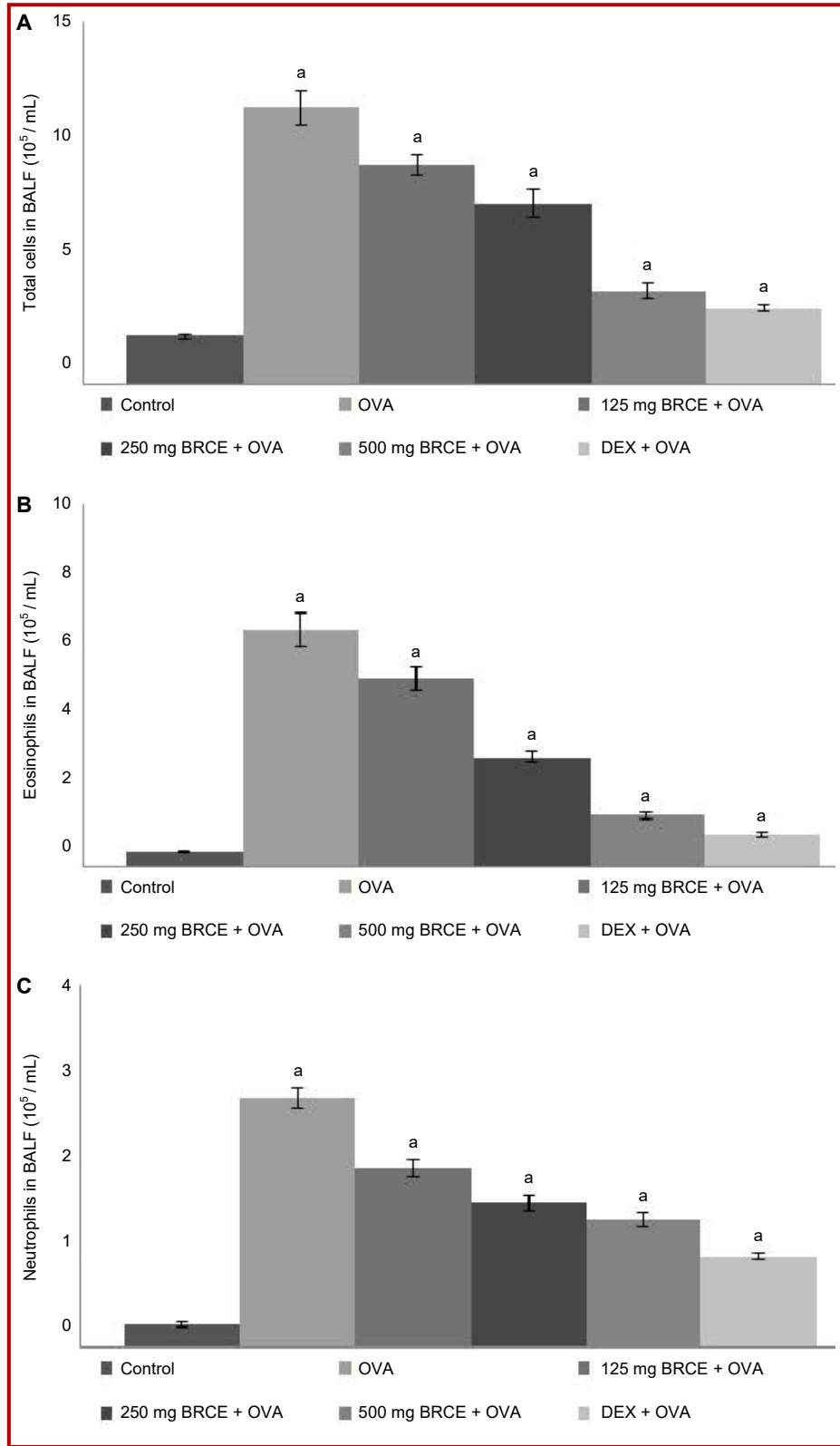


Figure 2: Effect of *Brassica rapa* extract on cell accumulation in BALF

*Brassica rapa* extract suppressed the total cell counts (A), eosinophils (B) and neutrophils (C) in BALF; Values are represented as mean  $\pm$  SD; n=6; <sup>a</sup>represents p<0.05 compared with control as determined by one-way ANOVA

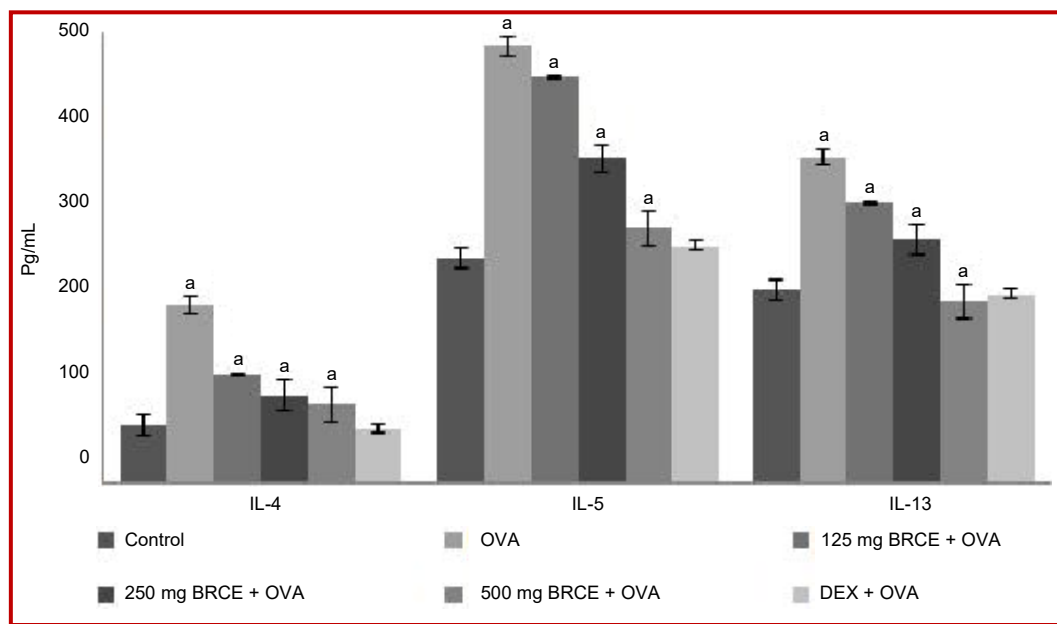


Figure 3: Effect of *Brassica rapa* extract on Th2 cytokine levels

Values are represented as mean  $\pm$  SD; n=6; \*represents  $p < 0.05$  compared with control as determined by one-way ANOVA

cytokines in relation to the OVA-challenged group (Figure 3). The same at 500 mg/kg dose reduced interleukin levels similar to DEX.

Asthma is characterized by a non-specific AHR and is defined as excessive narrowing of airways in response to a variety of contractile agonists including OVA. Airway hyper-responsiveness was assessed by measuring Cdyn and RI in response to increasing doses of methacholine administration in mechanically ventilated mice. Cdyn refers to the distensibility of the lung and is defined as the change in volume of the lung produced by a change in pressure across the lung. RI is defined as the pressure driving respiration divided by flow. OVA-challenged mice developed AHR, typically reflected by high RI and low Cdyn (Figure 4A and 4B). Treatment with *B. rapa* extract reduced RI and restored Cdyn in OVA-challenged mice in response to methacholine.

Asthma development is associated with NF- $\kappa$ B activation that leads to airway inflammation. The MAPK pathway has been reported to play a major role in biological responses, including cytokine expression. The effect of *B. rapa* extract on MAPK and NF- $\kappa$ B activation was investigated. The lung tissues were collected 24 hours after the final airway OVA challenge, and total and nuclear proteins were extracted. The expression of phosphorylated ERK, JNK, p38, I $\kappa$ B- $\alpha$  and nuclear p-NF- $\kappa$ B p65 and ERK, JNK, p38 in mouse lung tissues are shown in Figure 5 and 6. *B. rapa* extract suppressed phosphorylation of I $\kappa$ B- $\alpha$  in lung parenchyma, and attenuated nuclear localization of p-NF- $\kappa$ B p65. Furthermore, treatment with *B. rapa* extract inhibited the phosphorylation level of ERK and p38 signal pathways, but up-regulated phosphorylation of JNK.

We found that *B. rapa* extract at 500 mg/kg blocked ERK phosphorylation and p38 more effectively than lower doses (Figure 5 and 6).

## Discussion

The early airway response in asthma is IgE dependent and caused by the activation and degranulation of pulmonary mast cells by allergen mediated cross-linking of IgE antibodies bound to the high affinity IgE receptor (Fc $\epsilon$ RI). Th2 cytokines, including IL-4, IL-5, and IL-13, have been demonstrated to play an important role in the pathogenesis of airway inflammation and responsiveness in animal models and human (Wills-Karp, 1999; Busse and Lemanske, 2001). Th2 responses are triggered by allergen exposure in the airway via activating inflammatory cells and up-regulating IL-4, IL-5 and IL-13 expressions (Bisset and Schmid-Grendelmeier, 2005), which in turn lead to and/or related to airway infiltration, eosinophil activation, IgE production and mucus secretion and AHR as well (Grunig et al., 1998; Larche et al., 2002; Ngoc et al. 2005; Desai and Brightling, 2012). OVA-induction resulted in a marked rise in airway infiltration of inflammatory cells that was efficiently reduced by *B. rapa* extract.

In various allergic disorders as asthma, IL-4, IL-5 and IL-13 production levels have been reported to raise markedly (Busse et al., 1995; Cohn et al., 1998). The observed results are in line to the previous studies. The raised IL levels following OVA-challenges were significantly reduced by *B. rapa* extract.

Additionally, IL-4 has been demonstrated to stimulate

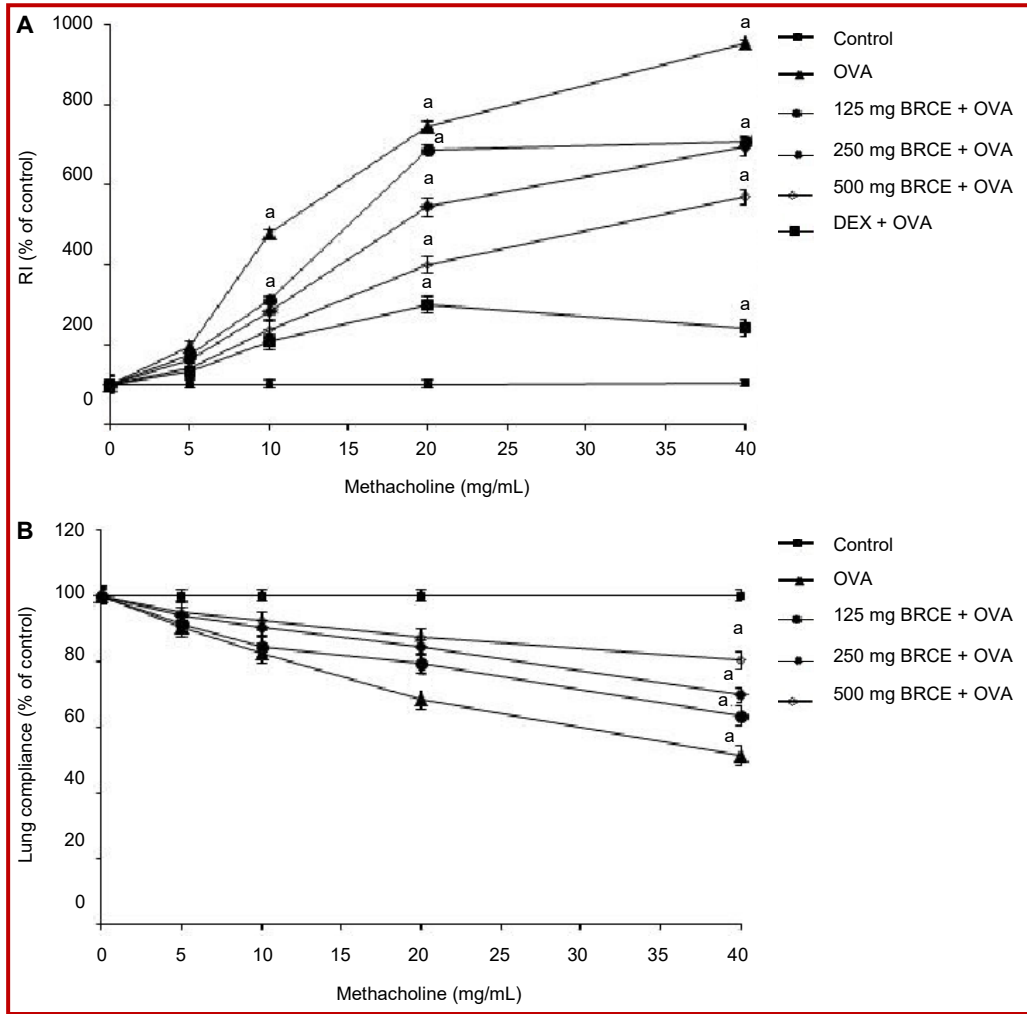


Figure 4: Effect of *Brassica rapa* extract on AHR

Values are represented as mean  $\pm$  SD; n=6; \*represents  $p < 0.05$  compared with control as determined by one-way ANOVA

isotype switching in B cells causing the switch from IgG to IgE production (Fish et al., 2005). IL-5 has been reported to be essential for eosinophils activation and survival, and in the development of AHR (Kips et al., 2001). Since IgE levels are dependent on IL-4 and IL-5 and are considered as an additional index of Th2 cytokine secretion in the pathogenesis of asthma, we measured the IgE levels. IgE has also been a key target in developing antiasthma strategies and clinical trials involving the neutralization of IgE have demonstrated satisfactory results in treating asthmatics (Busse and Lemanske, 2001; Hendeles and Soreness, 2007). In our study, *B. rapa* extract effectively suppressed IgE levels; this could be due to the direct effect of *B. rapa* extract or via suppression of ILs. Therefore, the reduction of IgE and Th2 cytokines may account for the improvement in OVA-induced asthma.

AHR is a clinical hallmark of asthma, which is defined as the abnormal increase in airflow limitation in response to the stimulus. During allergic inflammation,

the development of AHR was associated with inflammatory mediators (Berend et al., 2008). Our data suggested that *B. rapa* extract was able to effectively attenuate OVA-induced AHR which may be possibly related to suppression of IL-5 (Gleich, 2000).

NF- $\kappa$ B is a critical transcription factor for Th2 cell differentiation (Das et al., 2001; Siebenlist et al., 2005). NF- $\kappa$ B as a central regulator of both innate and adaptive immune responses exerts its function via the induction of genes that promote inflammation, leukocyte migration and activation. Studies have demonstrated that NF- $\kappa$ B activation modulates allergic inflammation responses (Alcorn et al., 2010). In unstimulated cells, however, NF- $\kappa$ B is sequestered in the cytoplasm by I $\kappa$ B inhibitory proteins (Juneja and Parmar, 2013) on activation, NF- $\kappa$ B unit p65 dissociates from the cytoplasm to the nucleus, leading to the synthesis and release of pro-inflammatory cytokines (Akira et al., 2001; Boulanger et al., 2003).

NF- $\kappa$ B activation has been reported to occur rapidly in

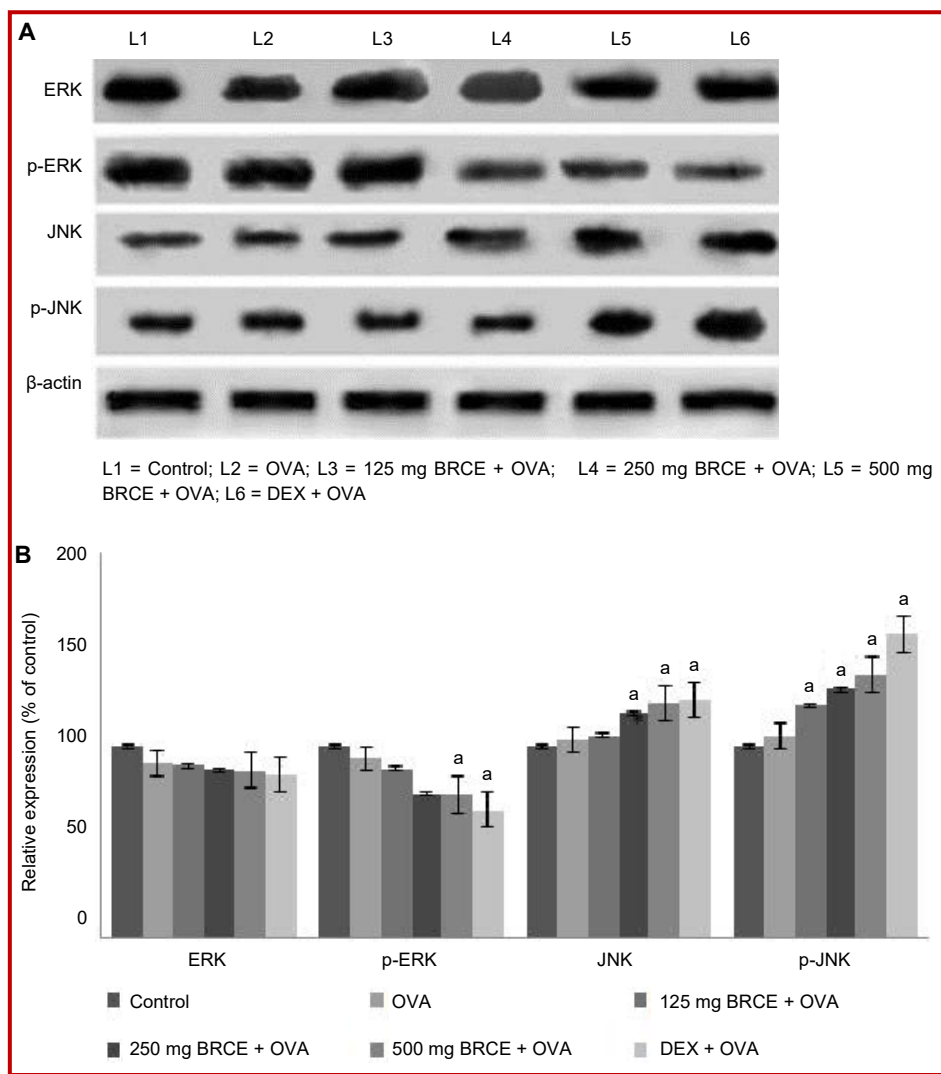


Figure 5: Influence of *Brassica rapa* extract on the expression of ERK and JNK signalling proteins

(A) *Brassica rapa* extract modulated expressions of ERK and JNK proteins (B) Relative expression values are represented as mean  $\pm$  SD; n=6; \*represents  $p < 0.05$  compared with control as determined by one way-ANOVA

the OVA-induced pulmonary inflammation model (Poynter et al., 2002). In our study, we demonstrated that OVA-induced p-NF- $\kappa$ B p65 activation and translocation from the cytoplasm to the nucleus was strongly inhibited by *B. rapa* extract treatment. The phosphorylation of I $\kappa$ B $\alpha$ , were regulated in *B. rapa* extract treated mice.

Recent studies have reported a raised p38 MAPK and ERK activity in the lungs of asthmatic mice (Kumar et al., 2003). In OVA-sensitized and exposed animal models, a p38 MAPK inhibitor effectively suppressed eosinophilic inflammation in the lungs (Underwood et al., 2000). JNK activity has been shown to be associated with IgE switching (Jabara and Geha, 2005). Therefore, MAPK is a key mediator of allergic diseases. Thus, blockade of p38 MAPK has been shown to have an anti-inflammatory effect in allergic asthma, suggesting that the inhibition and/or regulation of p38 MAPK could

possibly be essential for minimizing asthmatic symptoms (Duan et al., 2005). Our results showed that *B. rapa* extract effectively regulated the activation of p38 and ERK, but had a negligible effect on JNK. This suggests that the inhibition of p38 and ERK may have potential benefit in the therapy of asthma.

To summarise *B. rapa* extract inhibited the activation of NF- $\kappa$ B and MAPK, and reduced inflammatory cytokine and chemokine levels. These findings support a novel therapeutic use of *B. rapa* extract in the treatment of asthma.

*B. rapa* extract effectively improves AHR, inhibits Th2 cytokines and inflammatory cell infiltration. *B. rapa* extract also suppresses p38 MAPK and subsequently disrupts NF- $\kappa$ B activity. Thus by potentially reversing the features of asthma, *B. rapa* has proven to be a novel candidate for asthma treatment.



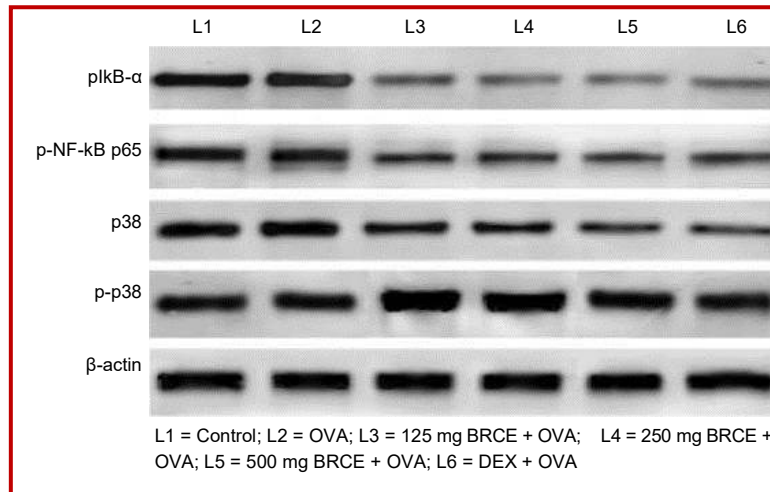


Figure 6: *Brassica rapa* extract modulated expressions of p38, IκB-α and nuclear p-NF-κB p65

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## Ethical Issue

All animal experiments were performed in accordance with the guide for the Care and Use of Laboratory Animals published by the US National Institute of Health.

## Conflict of Interest

Authors declare no conflict of interest

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**Author Info**

Fang Wang (Principal contact)  
e-mail: fangwang188@gmail.com