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Anredera cordifolia Extract in Reducing Immunoglobulin E Expression in Wistar Rats Allergic Model

Asti Widuri[1,2]*, Bambang Udji Djoko Rianto[3], Luh Putu Lusy Indrawati[3], Didik Setyo Heriyanto[4] and Rifki Febriansah[5]

1. Doctoral Program, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
2. Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Yogyakarta, Indonesia
3. Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
4. Department of Anatomic Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
5. Department of Pharmacy, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Yogyakarta, Indonesia

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*Corresponding author
Asti Widuri

Email:
astiwiduri@gmail.com

ABSTRACT

Allergic rhinitis (AR) is a prevalent health issue worldwide, characterized by an inflammatory condition of the nose mediated by immunoglobulin E (IgE). *Anredera cordifolia* (AC), the binahong plant in Indonesia, has been extensively used in herbal medicine since ancient times. AC contains secondary metabolites, such as flavonoids, with anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties. Many flavonoid compounds with anti-inflammatory activity can potentially treat nasal inflammation, such as allergic rhinitis. Quercetin, a natural polyphenol flavonoid, has anti-allergic mechanism by inhibiting histamine synthesis, regulating Th1/Th2 balance, and reducing Ig E antibody production in B cells. This study aims to determine whether there is a decrease in IgE expression after administration of AC extract in the Wistar rats allergic model. The research was conducted on 36 Wistar rats classified into nine groups: control group without any intervention (K1), negative treatment group (K2), positive standard treatment group (K3), treatment group with hydrogel intranasal AC extract of 2.5% (P1), 5% (P2), and 7.5% (P3), and treatment group with oral AC extract of 25 mg/200 g BW (P4), 50 mg/200 g BW (P5), and 75 mg/200 g BW (P6). Afterward, Ig E expression analysis was performed using ELISA. The t-test results for treatment groups applied with hydrogel intranasal AC extract of 2.5% revealed a significant difference in decreasing IgE levels before and after treatment. In conclusion, the finding supports that AC extract exerts its anti-allergy properties by suppressing IgE levels in the Wistar rats allergic model.

Keywords: *Anredera cordifolia*, anti-inflammatory, nasal administration, toxicity

INTRODUCTION

Allergic rhinitis (AR) is a prevalent health issue worldwide. In individuals who are sensitive to specific allergens, AR can be triggered by those allergens. AR is characterized by an inflammatory condition of the nose mediated by immunoglobulin E (IgE). The medical condition is distinguished by one or more cardinal symptoms, such as sneezing, itching, nasal congestion, and rhinorrhea (Passali et al., 2018; Wise et al., 2018). In addition to primary nasal symptoms, AR is often accompanied by secondary chronic or recurrent symptoms, including snoring, mouth breathing, ocular itching, tearing, and olfactory or auditory dysfunction. The symptoms lead to sleep disturbance, diurnal fatigue, and irritability, which affecting emotional and social aspects of quality of life in daily living (Komnos et al., 2019; Meltzer, 2001; Rosario et al., 2021).

IgE plays an essential role in the pathophysiology of allergic rhinitis. Atopic individuals will produce a specific allergen IgE when they are exposed to allergens. IgE receptors on basophils in the peripheral blood and mast cells in the respiratory mucosa will bind to IgE antibodies. When the same allergen is then inhaled, the IgE antibodies become linked to the cell surface by the allergen. This causes the release of chemical mediators, which results in the symptoms of allergic rhinitis (Allam et al., 2018; Eifan & Durham, 2016).

Allergic rhinitis management aims to minimize or eliminate symptoms to reduce suffering and improve the quality of life (Dubey et al., 2019). AR treatment options are pharmacologic (antihistamines, steroids, montelukast inhibitors, and biologics) and non-pharmacologic; however, these manage merely long-term relief of symptoms, do not cure the disease, and can fail occasionally. It highlights that numerous studies conducted for new potential agents for the allergic diseases are required because there has been a worldwide surge in demand for herbal healthcare products (Licari et al., 2019).

Pharmacologic treatment, such as antihistamines, anti-leukotrienes, biologic agents, and immunotherapy, are designed to modulate mast cells and their mediators. However, further research is essential to identify new therapeutic targets that can effectively reduce mast cell driven inflammatory responses (Zoabi et al., 2022). Additionally, active components in herbal medicine have demonstrated the ability to regulate mast cells immunological activity (Jafarinia et al., 2020).

Prolonged use of conventional medicines containing chemical drugs can have adverse effects on the body. The potential side effects on chronic diseases treatment have led to many studies to find new alternative therapeutic agents. Medicinal plants have a promising potential to provide symptoms relief in allergic diseases (Rahim et al., 2021). Meta-analysis study showed the herbal medicine effect in decreasing allergic rhinitis symptoms, and improving quality of life with no different outcome comparable to standard treatment. Although, the beneficial effects did not persist after 3 months. Herbal medicine can play a complementary role as an adjunct to standard treatment, enhancing therapeutic outcome and reducing the need for conventional medication (Hoang et al., 2021).

In this case, *Anredera cordifolia* contains various chemicals, including terpenoids, steroids, glycosides, flavonoids, saponins, and alkaloids (Leliqia et al., 2017). The most well-defined characteristics of all flavonoid groups are their antioxidant effects (Bahtiar et al., 2021). Flavonoids can modulate several stages of inflammation and have potential health benefits in chronic diseases such as AR (Rahim et al., 2021). Apart from its antioxidant properties, this substance exhibits a range of biological advantages, including anti-proliferative, anti-inflammatory, anti-viral, anti-thrombotic, anti-atherosclerotic, anti-tumoral, anti-ototoxic, and anti-allergic effects (Bari et al., 2019). In the current research, the authors sought to determine whether AC has anti-allergic therapeutic activity by decreasing IgE levels after AC extract administration in the Wistar rats allergic model.

MATERIALS AND METHODS

Materials

The study was conducted within the confines of a laboratory environment at LPPT UGM Unit 4, Gadjah Mada University, utilizing a pre-post control group design. The sample for this study consisted of 36 Wistar rats aged 2-3 months with healthy physical condition and body weight in the range of 150-300 g. The sample size was calculated bases on the principal of replacement, reduction and refinement. With nine groups, two repeated measurements and the requirement for sacrifice, the minimal number of subjects per group was determined to two. The rats in the experiment were subjected to a one-week acclimation period in a clean cage. Each group of rats was housed separately. They were kept under control under controlled environmental conditions, including a 12-hour light/dark cycle, a temperature of 23 °C and a relative humidity of 50%. They were also provided with standard rat chow pellets and water ad libitum. Moreover, this present investigation received ethical clearance from the health research ethics committee of the Faculty of Medicine and Health Science, Universitas Muhammadiyah Yogyakarta, as evidenced by the ethics certificate number 071/EC-KEPK FKIK UMY/XII/2021.

Wistar Rats Models of OVA-Induced Allergic Airway Disease

This study used an acute rat allergic model, where prior studies have demonstrated that brief exposure to ovalbumin can induce initial remodeling alterations. After a short duration, goblet cell hyperplasia and epithelial thickening were observable. Sensitization-challenge protocols for the acute model were by intraperitoneal injection of 100 µg Grade V chicken egg OVA (Sigma et al.) and 2 mg aluminum potassium sulfate (alum; Sigma Chemical) in 300 µl PBS on days 1, 7, and 14. Wistar rats were challenged for 30 minutes by nebulizing 1% (wt/vol) OVA in saline solution on days 21-26 before intervention (Locke et al., 2007).

***Anredera cordifolia* Extraction**

Anredera cordifolia simplistic leaf was obtained from CV. Merapi Farma Herbal, Hargobinangun, Pakem, Sleman, Yogyakarta, Indonesia. The plants were identified by the Biology Laboratory of the Faculty of Pharmacy at Gadjah Mada University. The botanical species investigated in the study was *Anredera cordifolia (Tenore) Steenis*, commonly known as binahong. The maceration technique was employed to 500 gr *Anredera cordifolia* leaf simplisia using 5 liters 96% ethanol for five days, followed by filtration through filter paper. The extract was dried using a rotary evaporator vacuum at 50 °C and then dried in a water bath at 50 °C. The AC leaf extract gel was formulated for nasal administration using a composition consisting of 1 g carbopol, 1 g hydroxypropylmethylcellulose, 4 g glycerin, 3 g triethanolamine, 0.04 g Nipagin, 0.04 g Nipasol, varying concentrations of AC leaf extract, and Aq ad 40 g. The mixture concentration for each oral therapy was prepared daily before administration, while the intranasal cream prepared in advance for the entire 5-day intervention period.

Application of *Anredera cordifolia* Extract for Wistar Rats

The rats were divided into nine groups, with a sample size of four rats per group. The groups were classified as the control without any intervention (K1), the negative control rats allergic model without treatment (K2), and the positive control rats allergic model with antihistamine treatment (K3). The intervention rats were allergic model with nasal application AC extract of 2.5% (P1), 5% (P2), 7.5% (P3), and allergic model with oral AC extract of 25 mg/200 g BW (P4), 50 mg/200 g BW (P5), and of 75 mg/200 g BW (P6).

The procedures were four normal control rats (K1) were not induced by ovalbumin and were not treated, four negative control rats (K2) were induced by ovalbumin and were not treated, and four positive control rats (K3) were induced by ovalbumin and treated with an antihistamine. The other groups were the rats allergic model induced by ovalbumin then intervention with nasal application AC extract of 2.5% (P1), 5% (P2), and 7.5% (P3). And the last groups were the rats allergic model induced by ovalbumin then intervention with oral AC extract of 25 mg/200 g BW (P4), 50 mg/200 g BW (P5), and 75 mg/200 g BW (P6).

Determination of Total IgE Titres by ELISA

Serum of a minimal volume of 200 µL was obtained from the retro-orbital sinus of each rat under mild anesthesia, allowed to clot for 10-20 minutes at room temperature, centrifuged at 2000-3000 RPM for 20 minutes, and then its supernatant was collected without sediment. IgE ELISA kits produced for rats (Bioenzy BZ-08182540-EB) were used to measure plasma total IgE values in line with the manufacturer's instructions, expressing total IgE levels as KU/L.

Statistical Analysis

The data are presented as the mean ± standard deviation (SD) value. The data's normality was assessed using the Shapiro-Wilk test. The study employed the student t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data to detect significant differences. While one-tailed p-values were used, a statistical significance level of 0.05 was utilized to ascertain the significance of the results.

RESULTS AND DISCUSSION

After the intervention of each group with nasal application and oral extract of AC leaf was completed and before rats were anesthetized to take blood samples for total IgE examination, the researchers evaluated the function of nervus olfactorius using a food test. The test aims to measure the time the rats *take* to find a palette of food under the bedding layer. On the test day, rats fasted and watered ad libitum for 18 hours, and then each rat was placed in a clean cage containing 3 cm of clean bedding with a food palette 1 cm beneath. The timer was started and recorded the time spent finding the food. The result exhibited that intranasal application intervention groups had better olfactory function than rats with oral intervention. Nevertheless, the fastest-to-find food palette or the best olfactory function test result was found in rats in the antihistamine therapy group (Table I). The results promote intranasal administration potential of herbal materials for enhancing drug delivery over oral therapies by delivering greater concentrations, without first-pass metabolism and limiting systemic side effects.

Table I. The result of olfactory nerve function

Groups	Time (Minutes)
K1	3.6
K2	5.4
K3	1.3
P1	4.4
P2	3.0
P3	3.3
P4	4.5
P5	6.0
P6	5.0

The distribution of each group's mean and standard deviation of total serum IgE levels were evaluated after sensitization and after each treatment, and each group showed normally distributed data (Table II). Immunoglobulin E expression and histamine release that occur during the early phase are the important key features of AR pathophysiology. The elevated IgE levels observed before intervention were consistent with findings from mouse allergic model studies. Adequate sensitization was evaluated in acute, sub-acute and chronic models using OVA sensitization and aerosol challenge compared to control mice treated saline. Notably, OVA-specific IgE titres were highest in the chronic model, which received an extended aerosol challenge (Locke et al., 2007).

The Effect of AC Extract IgE Levels of Wistar Rats Allergic Models

This study evaluated the anti-allergy effect of AC extract in the rat allergic model by suppressing IgE in each group (Figure 1). The paired t-test (Table III) displays that IgE levels in the pre-and post-tests found significant decreases in the Wistar rats' group with AC extract leaf intranasal application of 2.5% concentration. Anosmia or hyposmia are conditions that occur in patients with nasal infection or inflammation, such as rhinitis allergies (Gupta et al., 2019; Rosario et al., 2021). Therefore, the evaluation of olfactory function is a critical component for nasal therapeutic treatments. The buried food test is a dependable procedure for evaluating the sense of smell, which capitalizes on an animal's innate inclination to utilize olfactory cues for locating food and its capacity to detect volatile aromas. Rats possess the ability to differentiate between distinct scents and exhibit spatial orientation towards them (Thakurdesai & Deshpande, 2021). The study's findings indicate that the application of intranasal binahong cream resulted in improved olfactory function in all intervention groups (with times of 4.4, 3.0, and 3.3 minutes) compared to the rats in the control non-therapy group (with a time of 5.4 minutes). However, the rats in the antihistamine medication group had the quickest time to discover food and the highest score on the olfactory function test (1.3 minute) (Table I).

The impairment of the sense of smell in rats with an allergic rhinitis model is associated with a type I hypersensitivity reaction mediated by IgE. This reaction is characterized by an excessive production of type 2 cytokines and an accumulation of eosinophils in the affected tissues. The mechanism involves the release of inflammatory mediators by lymphocytes and macrophages, which are known to stimulate excessive secretion from the respiratory and Bowman's glands. Excessive production of nasal mucus can cause changes in the levels of ions, which can impact the environment around olfactory neurons and the process of transduction (Ozaki et al., 2010). The study's findings indicate that rats in the control group, who did not undergo intraperitoneal sensitization or OVA inhalation challenge, took less time to retrieve buried food compared to the untreated allergic model rats (3.6 vs 5.4 minutes, Table I).

Allergic rhinitis is caused by an immune system imbalance (Th1/Th2), which leads to the excessive production of Ig E antibodies by B cells. We created a mouse model of allergy by following a previously established experimental approach with some minor adjustments. After OVA sensitization and intranasal allergen challenge, we built the mouse model of allergy using the experimental methodology previously reported, but with a few minor modifications (Fu et al., 2017; Locke et al., 2007). The mean and standard deviation of total serum IgE levels for each group were assessed during sensitization and after each treatment (Table II).

Table II. Homogeneity test for measurement of the total of IgE (mean ± SD)

Groups	IgE Before Intervention	Normality	IgE After Intervention	Normality
K1	09.00±0.49	0.564	07.95±0.99	0.375
K2	10.07±0.73	0.064	08.84±1.34	0.260
K3	08.03±0.65	0.960	07.50±2.97	0.790
P1	09.99±0.84	0.945	08.75±0.91	0.058
P2	08.03±0.86	0.522	08.22±0.32	0.222
P3	08.44±1.11	0.591	07.98±0.55	0.822
P4	08.40±0.47	0.991	06.78±2.62	0.196
P5	08.59±0.99	0.585	08.30±0.55	0.827
P6	08.10±0.84	0.989	07.31±0.46	0.822

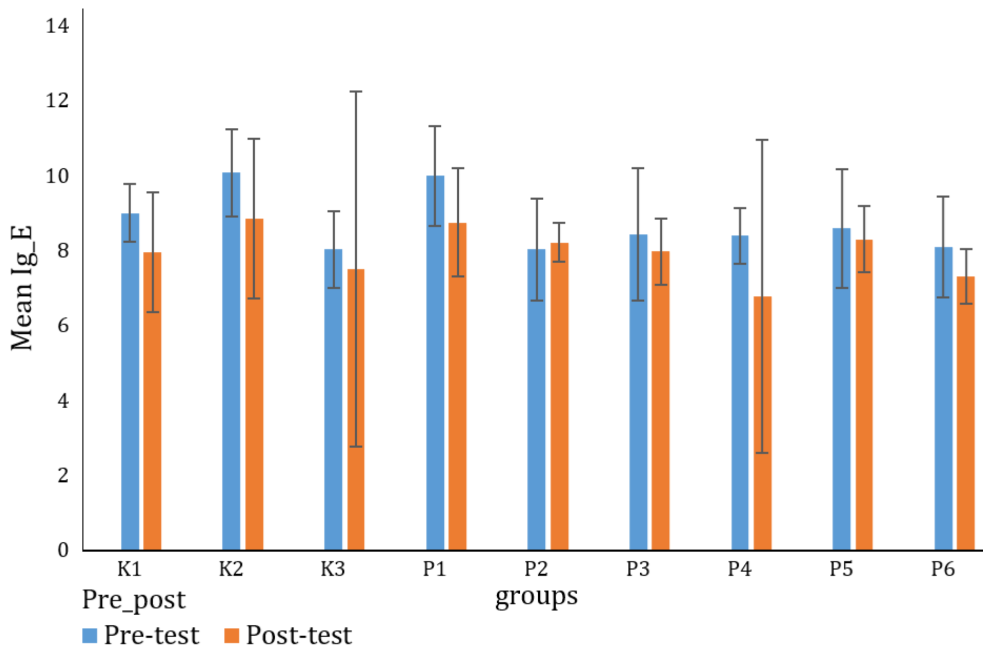

Figure 1. Total Ig-E pre-test and post-test of each group

While there are several modern drugs available, none of them has been guaranteed to be free from adverse effects. Various promising herbal treatments for allergic rhinitis are now available across the globe due to their low side effects and affordable price (Hoang et al., 2021). Many studies reported that biologically active ingredients of medicinal plants with antioxidant or anti-inflammatory properties, such as flavonoids and polyphenols, contribute to anti-allergic activity (Sim et al., 2019). *Anredera cordifolia* has been widely used in traditional herbal medicines, the phytochemical screening of AC leaves extract showed positive results to the presence of phenolic, steroid, terpenoid, alkaloid and saponin (Salim et al., 2021). In the present work the anti-allergy activity and possible of action of AC on an immunoglobulin (Ig) E- mediated allergy rats model has been studied. The effect of the administration of binahong leaf extract oral and intranasal for 5 days on total IgE shown in figure 1. Although all treatment showed decreasing of total IgE, the nasal application 2.5% extract binahong showed significant decreasing (p=0.016) (Table III).

While the oral and intranasal application of AC extract demonstrated a reduction in IgE levels in a Wistar rat model of allergy, it is not possible to conclude that it has anti-allergic effects. This is because there was no clear relationship between the dose of the extract and the reduction in IgE levels. Additionally, the control group also showed a decrease in IgE levels (Figure 1).

Table III. Comparison of total serum IgE values before and after treatment among groups

Group	Pre-test		Post-test		Mean Difference	p-value
	Mean	**SD**	**Mean**	**S**		
K1	9.00	0.49	7.95	0.99	1.05	0.211
K2	10.07	0.73	8.84	1.34	1.23	0.098
K3	8.03	0.65	7.50	2.97	0.53	0.763
P1	9.99	0.84	8.75	0.91	1.24	0.016*
P2	8.03	0.86	8.22	0.32	-0.19	0.650
P3	8.44	1.11	7.98	0.55	0.46	0.415
P4	8.40	0.47	6.78	2.62	1.62	0.309
P5	8.59	0.99	8.30	0.55	0.28	0.704
P6	8.10	0.84	7.31	0.46	0.79	0.260

However, the notable decrease in IgE levels indicates the potential of AC extract to have anti-allergic effects by inhibiting the granulation of mast cells through the action of polyphenolic compounds, such as flavonoids. This aligns with the findings of Rakha et al., (2022), who posited that the presence of antioxidants and anti-inflammatory AC components plays a significant role in mitigating allergic reactions. Strong antioxidant qualities raise the activity of the antioxidant enzymes catalase and erythrocyte superoxide dismutase while lowering the blood level of IgE antibodies (Han et al., 2017; Shams et al., 2021).

Herbal medicine has been shown as anti-allergic properties by inhibiting the release of histamine, leukotrienes, cytokines, and chemokines from inflammatory cells. Additionally, active compounds in herbal have been found to modulate the immunological response of mast cells (Kotov et al., 2022; Rahim et al., 2021). For instance, the *Shenqi* traditional Chinese polyherbal medicine exhibits anti-allergic activity by inhibiting the mast-cell-mediated allergic response and enhancing the Th1/Th2 ratio balance in individuals with allergic rhinitis (Shao et al., 2017). As biological agents with antioxidant and anti-inflammatory characteristics, hesperidin and thymol significantly reduced serum IL-5, IL-13, and IgE levels in the rats' allergic models. Other herbal medicines worldwide with anti-allergic mast cell modulation include *Glycyrrhizic acid* (Han et al., 2017). *Cordyceps sinensis* (Chen et al., 2020), *Lamiaceae* (Sim et al., 2019), *Asarum heterotropoides* (Choi et al., 2021), *Yupingfeng* (Chen et al., 2021), bee pollen phenolic extract (Medeiros et al., 2008), and *Clinacanthus nutans* (Kow et al., 2023).

CONCLUSION

It is the first study showing the anti-allergic effects of *Anredera cordifolia* extract oral and intranasal in an experimental rat model of allergic rhinitis sensitized using ovalbumin peritoneal and inhalation. It was found that decreasing IgE levels before and after the application of AC extract were significantly different in the intranasal group at a 2.5% concentration. Based on the research outcomes, additional experimental and clinical trials are required to investigate the efficacy of AC utilization in managing allergic rhinitis.

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AUTHOR CONTRIBUTIONS

Asti Widuri designed and performed the research, data analysis, and manuscript writing. Rifki Febriansah aided with the experiments and did the statistical analysis and data visualization. Bambang Udji Djoko Rianto, Luh Putu Lusy Indrawati, and Didik Setyo Heriyanto provided critical manuscript revisions. The final text has been reviewed and approved by all authors.

CONFLICT OF INTEREST

The authors certify that there are no competing interests to consider.

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