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RESEARCH ARTICLE

ANTIHISTAMINIC EFFECT OF THE AQUEOUS EXTRACT OF *ALLIUMCEPA* (LILIACEAE) IN THE MOUSE MUS MUSCULUSOF SWISS LINE

Tovi, W. M. O., Komenan, E. O. P. K., Irie BI, B. B. and Kouakou, K.

Laboratory of Biology and Health; UPR Reproduction and Animal Development; Université Félix Houphouët-Boigny Abidjan Côte d'Ivoire

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Corresponding author:
Chhaya D. Badnakhe

ABSTRACT

Objective: *Alliumcepa* is often used in traditional African medicine for the management ofmany pathologies. Therefore, our objective was to study the anti-histaminic effect of the aqueous extract of *Alliumcepa* in mice. **Material and Methods:** Allergy was previously induced in mice by administration of an allergic solution (0.15 ml egg white, 0.05 ml maalox and 0.05 ml NaCl) intraperitoneally. The antiallergic effect of the Total Aqueous Extract (TEA) of *Allium*cepa leaves was evaluated by observing the number of scratching in allergic mice treated orally with different doses (250 and 500 mg/kg of body weight) of this extract. **Results:** The phytochemical study revealed the presence of polyterpenes, sterols, polyphenols, flavonoids, tannins, quinone and alkaloids but also the absence of saponosides. The acute toxicity study at the single dose of 2000mg/kg CP orally revealed that the aqueous extract of *Alliumcepa* is not toxic and would have an oral LD 50 greater than or equal to 5000mg/kg CP. After oral administration of the extarit, we observe a reduction in the number of scratching in allergic mice. **Conclusion:** These results show that *Alliumcepa* bulbs have an anti-allergic activity, which would justify its use in African traditional medicine to prevent or treat allergy.

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INTRODUCTION

The prevalence of allergic diseases has been constantly increasing in the world in recent years (1). According to the WHO, nearly 30% of the world's population is affected by this disease compared to 3.8% in 1968. By 2050, one person in two will suffer from this disease. It is now the fourth most common chronic disease in the world after cancer, AIDS and cardiovascular diseases (2). To face this disease, treatments have been implemented such as specific immunotherapy which has proven its effectiveness by allowing the avoidance of allergens, pharmacological treatments such as antihistamines and corticoids (3). However, although pharmacological treatments relieve symptoms, they are accompanied by notable side effects such as liver cancer. Therefore, in developing countries, the population faces many difficulties in treating allergic diseases such as difficult access to health centers, lack of qualified personnel, expensive treatments and lack of hospital infrastructure (4).

In order to overcome all these difficulties, researchers have increased their research on the therapeutic power of plants against allergic diseases. With this in mind, we chose the vegetable *Allium cepa* (onion) which is described as a miracle plant in the therapeutic sphere. *Allium cepa* is recognized as an important source of valuable phytonutrients such as flavonoids. Flavonoids ubiquitous in vegetables and fruits have shown several biological effects, including anti-oxidant, anti-inflammatory, anti-cancer, and anti-diabetic activities (5). Therefore, the objective of the present study was to evaluate the antihistaminic effect of the total aqueous extract of *Allium cepa* on allergic mice.

MATERIALS AND METHODS

Materials

Plant material : The plant material is essentially *Allium cepa*, was purchased at the Gouro market of Adjamé in the district of Abidjan on August 2021.

Animal material : The animal material consists of 26 Swiss mice strain with eight weeks of age and weighing between 18 and 22 g: six nulliparous and non-pregnant mice are used for the acute toxicity test (OECD 423) and 20 mice for the pharmacological test.

Chemical material : In addition to the Total Aqueous Extract (TAE) of *Allium cepa*, an allergen was used to conduct this experimental study. This is egg white which contains ovalbumin, maalox which is used as a supplement containing aluminum hydroxide and NaCl0.9% and HYDROCORTISONE UPJOHN, a drug commonly used in the treatment of allergic diseases.

Technical equipment : The technical equipment consisted of an electric grinder, SMART brand mixer, a precision balance (YP series, China) for weighing the mice and the different substances (maximum 300g; minimum 0.001g), white cloth and absorbent cotton for filtering, insulin syringes for intraperitoneal injection, five gastric probes for administering the different solutions obtained to the animals, a camcorder (cell phone) for observing the scratching frequency.

Methods

Method of extraction : After purchase, *Allium cepa* bulbs are washed and cut into small pieces. One hundred grams (100g) of *Allium cepa* was macerated in 1 liter of distilled water for three times three minutes in the blender. The macerate was filtered twice on white square cloth and then successively on absorbent cotton. The filtrate obtained was evaporated in an oven at 50 °C for 48 hours to obtain a dry extract (6).

Phytochemical screening study : This study consists in determining some chemical groups present in the E.T.A. We characterized the various chemical groups by referring to the techniques described by (Békro *et al*., 2007) (7) and (N'guessan *et al*., 2009) (8). The phytochemical screening will focus on etheric, methanolic and aqueous extracts.

Acute toxicity study : This experimental study aims to evaluate the acute oral toxicity of *Allium cepa* E.T.A. by determining the Lethal Dose 50% (LD50). It has been adapted to the one described by the guideline 423 (9). It is based on a sequential process that uses a minimum number of animals per step (three animals). For the initial dose, one of four levels is chosen: 5, 50, 300 and 2000 mg/kg CP. The level chosen is the one at which mortality can be expected among some of the treated animals. Thus, given the common use of Allium cepa in traditional medicine and its nutritional properties, 2000 mg/kg CP is chosen as the initial dose in female mice.

For the first stage of this study, two batches of three mice are formed:

- **Batch 1:** mice receiving 2000 mg/kg of PC from Allium cepa E.T.A.;
- **Batch 2:** control mice receiving distilled water (10 ml/kg of PC).

However, prior to the administration of the test substance, these animals are fasted, food but not water is removed for 3 to 4 hours. After the fasting period, the animals were weighed and then the test substance was administered to them. After administration of the substance, the animals were again deprived of food, for 3 to 4 hours.

The animals are observed individually for the first 30 minutes and regularly for the first 24 hours after treatment. Special attention is required during the first 4 hours and daily for 14 days after administration of the substance. The main signs looked for include:

- Excitement,
- Breathing difficulties,
- Food refusal,
- Oral and/or nasal bleeding,
- Convulsion,
- Trembling,
- Diarrhea,
- Coma,
- Death.

The individual weight of each mouse, determined shortly before administration of the test substance, is taken at least once a week.

Pharmacological study : This study was divided into two parts, namely the induction of the allergic reaction and the effect of Allium cepa E.T.A in allergic Swiss mice.

Induction of the allergic reaction : The induction of allergic reaction was done with 20 Swiss mice which were divided into five batches of four mice:

- **Lot 1:** Control mice receiving 10 ml/kg body weight of NaCl 9‰
- **Lots 2,3,4,5,:** These mice each received 0.25 ml of allergic solution (0.15 ml egg white, 0.05 ml maalox and 0.05 ml NaCl). This mixture represents the allergic solution.

The allergic solution was administered intraperitoneally. Mice received the first sensitizing dose on day 0. The second and third sensitizing doses of the allergic solution were administered on day 3 and day 6. Mice were weighed throughout the induction period.

Effect of Allium cepa E.T.A. in allergic swiss strain mice: This test includes mice that responded favorably to allergy induction that are grouped into four batches as well as healthy mice in one batch.

- **Batch 1:** positive control (PC) mice receiving distilled water at 10 ml/kg PC.
- **Batch 2:** negative control (NC) mice receiving distilled water at 10 ml/kg PC
- **Batch 3:** referent control mice (RT) received HYDROCORTISONE molecule at 5 mg/kg PC
- **Batch 4:** mice treated with Allium cepa E.T.A. at a dose of 250 mg/kg PC
- **Batch 5:** mice treated with Allium cepa E.T.A. at a dose of 500 mg/kg PC.

This test was performed over a period of seven days with daily administration of the different substances.

Observation of the number of scratches: Observation of the number of animal scratches began at the time of the third sensitizing dose and ended on the last day of the pharmacological study 30 min after the administration of the

sensitizing dose or gavage of the animals. Subjects were observed with a video camera in an isolated, lighted area for 15 min.

Statistical analysis of the data: Statistical processing of the results is performed using GraphPad Uninst_Prism 8 software. The results are given as the mean followed by the standard error on the mean (mean ± SEM). The analysis of variance (ANOVA) was used to compare the means obtained. This software is also used to obtain the graphs.

RESULTS

Chemical groups present in Allium cepa bulbs

The results of the phytochemical analysis allowed to highlight the presence or absence of some or absence of certain groups of chemical compounds of therapeutic interest (Table I). (Table I). Polyterpenes, polyphenols, flavonoids, tannins, quinones and alkaloids are the chemical compounds revealed by these analyses. Their presence in the A.T.E. of *A. cepa* is relatively abundant. However, this extract does not contain saponosides.

Acute toxicity evaluation: determination of the Lethal Dose 50% (LD50) : Oral administration of 2000 mg/kg CP of *Allium cepa* T.E. (Table II). This dose of 2000 mg/kg CP would also have no significant effect ($p>0.05$) on the weight of the animals compared to control animals receiving distilled water (Figure 1). No deaths occurred in the animals and no clinical signs of toxicity were observed. Thus, *Allium cepa* would have an LD50 of between 2000 and 5000 mg/kg CP or greater than 5000 mg/kg CP according to the OECD 423 guideline.

Recorded signs of allergy: The study developed a model of food allergy in swiss mice. For this purpose, they were sensitized to an allergic solution by three intraperitoneal injections of 0.25 ml dose (0.15 ml egg white, 0.05 ml Maalox and 0.05 ml NaCl 9%) over a period of seven days. These injection results showed the presence or absence of the allergic reaction (Table Ⅲ). The allergic symptoms are evaluated and scored follows the observation of 30 min after injection from the third sensitizing dose of the allergic solution. We observed signs such as scratching and reduced activity (motor skills) in mice after the second sensitizing dose.

Effect of Allium cepa total aqueous extract in allergic mice: Mice are treated daily for seven days by gavage (oral) administration of 250 and 500 mg/kg CP of total aqueous extract (TAE) of Allium cepa and intraperitoneally for Hydrocortisone in these mice. One week after treatment, the mice are sensitized to A.cepa T.E.A and Hydrocortisone. The results are shown in Figure 2 with different variations in the number of scratches in these mice. In the control mice receiving only 0.9% NaCl by IP, the number of scratching did not vary significantly ($p<0.05$) throughout the experimental study (seven days) and this number remained at 5±1.08. On the other hand, 30 min after intraperitoneal injection of the combination of different products forming the allergic solution (0.25 ml), we notice a significant increase ($p<0.05$) in the number of scratching in all mice. This number of scratching which was 5±1.08 increases to 8±0.70.

In order to observe the number of scratching again, we applied a treatment with different test substances such as hydrocortisone of 5 mg/kg CP and A.cepa E.T.A of 250 and 500 mg/kg CP. After treatment, we do notice a decrease in the number of scratching depending on the dose given to the mice. However, with mice receiving distilled water (DW), this number of scratching does not vary throughout our experiment.

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As for our A.T.E. of A.cepa, the different doses of 250 mg/kg and 500 mg/kg of PC administered by gavage to mice cause a significant ($p<0.05$) decrease in the number of scratching. This decrease is more accentuated at the dose of 500 mg/kg of PC from the fifth day of treatment.and less for the dose of 250 mg/kg of PC compared to the reference control (hydrocortisone) Indeed, at the end of the experiment the decrease in the number of scratching reaches 61.53% for the dose of 250 and 76.92% for the dose of 500 mg/kg of PC (Table Ⅳ). The percentage of reduction in the number of scratching is almost the same for A. cepa E.T.A. as for hydrocortisone (reference solution).

Table 1. Highlighting of some secondary metabolites in the E.T.A. of Allium cepa

secondary Metabolism	Sterols	Polyphenols	Flavonoids	Tannins		quinonic substances	Alkaloids		Saponosides
Sub-units	Polyterpenes			Cat	Gal		B	D	
Type of answer	+ +	+	+ +	+	-	+	+	++	-

Gal: gallic(++): Abundant
Cat: catechetical(+): presence
D: DRAGENDORFF
B: BOUCHARDAT(-): lack

Table 2. Results of clinical signs in the acute toxicity test after 14 days of observation.

Clinical signs / Animal batches	Batch 1: Control (Distilled water)	Batch 2: treated (2000 mg/kg of CP)
Food refusal	-	-
Oral and/or nasal bleeding	-	-
Breathing disorders	-	-
Apathy	-	-
Excitation	-	-
Tremor	-	-
Diarrhea	-	-
Coma	-	-
Convulsion	-	-
Abdominal pain (contortion)	-	-
Dead	-	-

(+) : presence of clinical sign (-) : absence of clinical sign

		0	1	2	3
BATCH 1	S1		●		
	S2			●	
	S3			●	
	S4			●	
BATCH 2	S1			●	
	S2			●	
	S3			●	
	S4			●	
BATCH 3	S1			●	
	S2			●	
	S3		●		
	S4			●	
BATCH 4	S1		●		
	S2			●	
	S3			●	
	S4			●	
BATCH 5	S1			●	
	S2			●	
	S3			●	
	S4		●		

0 : no sign
1 : animals scratch between 4 and 10 times during 15 min
2 : animals scratch more than 10 times over 15 min, or show reduced activity
3 : death
S : Mouse

Table 4. Percentage reduction in the number of scrapings.

Batch type	Negative control (Water) Distilled	Positive Control Distilled Water	Reference Control Hydrocortisone 5 mg/kg	Treated E.T.A. *A.cepa* 250mg/kg	Treated E.T.A *A.cepa* 500mg/kg
% reduction of the Number of scratches	7	6	76,92	61,53	76,92

Effect of total aqueous extract of Allium cepa on the weight of allergic mice: Figure 3 shows the weight evolution of allergic mice after 7 days of treatment. It can be seen that the treatment of mice with the total aqueous extract of A. cepa does not lead to a significant variation ($p<0.05$) in body weight compared to those receiving distilled water or the allergen solution.

DISCUSSION

The present work focused on the study of toxicity and antiallergic effect. The acute toxicity study of E.T. A of A. cepa in swiss strain mice determined that this extract administered by the VO at the dose of 2000 mg/kg does not cause any clinical signs or mortality in mice for this single dose.

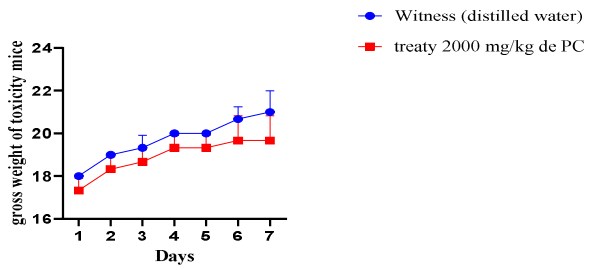
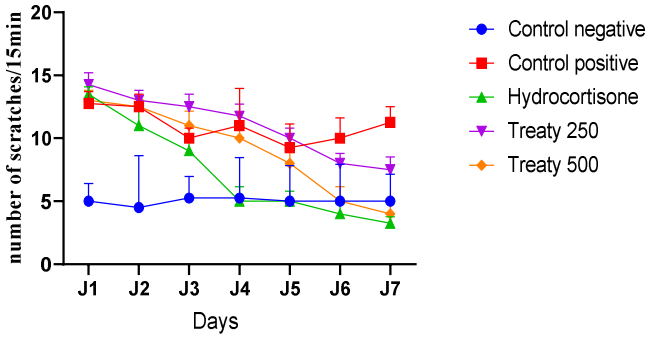


Figure 1: Variation in mouse body weight as a function of time. (Mean ± SEM, n = 4,) SEM: Standard error on the mean. Values are mean weights of mice during toxicity, n=4. ****p<0.0001: significantly different from control mice.



*p<0.05 **p<0.01: significantly different from negative control

Figure 2: Evolution of the number of scratches after treatment with different doses of A. cepa E.T.A. or hydrocortisone in Swiss strain mice Values are mean numbers of scratching, n=4

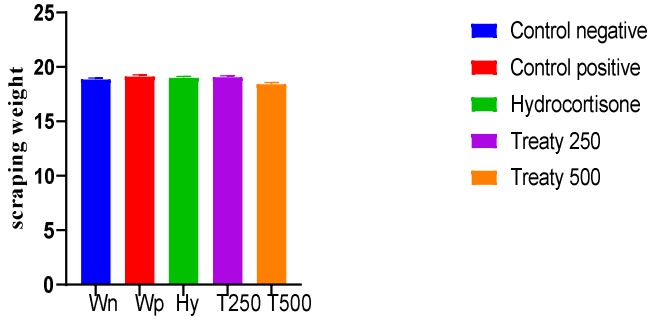


Figure 3. Effect of total aqueous extract of A.cepa on weight development of allergic Swiss strain mice

Indeed, the OECD 423 guideline indicates that the Lethal Dose 50 (LD50) of Allium cepa would be between 5000-10000 mg/kg of Allium cepa T.E.A according to the Hodge and Sterner scale. Studies by Corzo et al. (2007) (10), Minker (2012) (11) and Moraldi (2018) (12) on Allium sativum and A.cepa E.T.A in mice, rats and domestic carnivores have shown that the LD50 is greater than 5000 mg/kg PC. At the level of allergic symptoms, we observed signs such as scratching and reduced motor activity from the second sensitizing dose. These results are not in line with those of Perrier et al. (2009) (13) who describe deaths of some mice.

In this study, we tested the VO immunotherapy strategy for Allium cepa E.T.A and the PI immunotherapy strategy for hydrocortisone on allergic mice. The study of the effect of A.cepa E.T. A.cepa E.T. in allergic mice at different doses gave results indicating that A.cepa E.T.A. is endowed with anti-allergic biological activity. The gavage of A. cepa E.T. A.cepa E.T. to swiss strain mice caused a decrease in the number of scratching with treated mice compared to untreated mice (positive and negative control receiving distilled water).

Indeed, the treatment of our reference control with hydrocortisone, a drug commonly used against allergic diseases, allowed us to observe a significant decrease ($p<0.05$) in the number of scratching in mice. These different effects are dose-dependent with a maximum effect at a dose of 500 g/kg CP for E.T. A of A. cepa. These results correlate with the work of Shiwen et al (2017) (14), Ema.Europea (2012) (15) and Daniel et al (2007) (16) who asserted anti-allergic activity. According to Shiwen et al. (2017) (14) who studied the anti-allergic activity of glycyrrhizic acid on IgE allergic reaction by regulation of allergy-related immune cells, glycyrrhizic acid regulates the differentiation of cells. TH, which decreases the high level of TH2-related cytokine (IL-4) secretion to restore the TH1/TH2 immune system balance. It also affects antibody-producing B cells specific to ovalbumin solution and acts as a mast cell stabilizer to reduce mediator release through the inhibitory effect of Ca2+ influx due to the lower expression of calcium channel proteins. Upon initial contact with the body, the food allergen introduced through the digestive tract is taken up by antigen-presenting cells (APCs) including dendritic cells, macrophages or B lymphocytes. The allergen is degraded into peptides and after migration of APCs to the draining lymph nodes, this peptide is presented by the APCs via MHC class II to naive CD4+ T lymphocytes (TL). During an allergy, activated CD4+ T cells will differentiate into Th2-type CD4+ T cells. The increase in the population of CD4+ T cells of the Th2 type will create an imbalance in the immune system and in particular in the balance between the CD4+ T lymphocytes of the Th1 type and those of the Th2 type. These Th2 lymphocytes will secrete cytokines such as IL-4, IL-5 or IL-13 which will activate effector cells, mainly eosinophils and basophils. IL-4 also induces the maturation of B lymphocytes (LB) into plasma cells that secrete allergen-specific IgE. The IgE produced in large quantities during the sensitization phase binds to the FcεRI receptors present on the surface of mast cells and basophils, pre-activating them. However, this phase is said to be asymptomatic since the subject sensitized to the allergen does not present any symptoms. When the body encounters the allergen again, it rapidly binds to IgE antibodies in mast cells and basophils, leading to their degranulation and the release of inflammatory mediators. Numerous molecules are then released, such as histamine or tryptase, as well as cytokines or chemokines, more precisely IL-4, IL-5 or IL-13, which promote this phenomenon of inflammation by increasing vascular permeability, causing vasodilatation and local tissue degradation, and recruiting and activating other cells, such as eosinophils, which also release pro-inflammatory cytokines.

The use of IL-2 and IL-10 cytokines would stimulate Treg lymphocytes (17, 18) to rebalance the balance between Teff and Treg, which is in favor of Teff during allergy, with the aim of decreasing allergic symptoms and increasing tolerance to food allergens (19). As confirmed by active systemic allergic reaction, passive skin anaphylaxis, and RBL-2H3 cell-based immunoassay, our A.cepa E.T.A. exhibits antiallergic activity and can be used in the future as a potential antiallergic nutrient which correlates with the work of Shiwen et al. (2017)(14)

CONCLUSION

This study shows that the total aqueous extract of A.cepa administered orally, does not cause any mortality, nor any clinical signs for the single dose of 2000 mg/kg CP. Thus the

OECD 423 guideline indicates that the LD 50 of Allium cepa would be higher than 5000 mg/kg CP. The results of the study of the effects of Allium cepa total aqueous extract (TAE) on mice allergic to different doses of the said extract, indicate that Allium cepa has anti-allergic properties. Thus, the polyterpenes, polyphenols, flavonoids and alkaloids present in the E.T.A. of this vegetable could be at the origin of these pharmacological effects. In perspective, it would be interesting to :

- to determine the different populations of immune cells during the treatment of allergy,
- to study the subacute and chronic long-term toxicity of the total aqueous extract of Allium cepa,

ETHICAL APPROVAL

The animals were used under ethical and deontological conditions under the supervision of our supervisors.

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COMPETING INTERESTS: The authors have declared that there are no competing interests.

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