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# Analgesic Effect of *Ageratina adenophora* Ethanol Extract on Migraine Rat Model

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***Abstract:***

This study explored the effect of ethanol extract of *Ageratina adenophora* on migraine caused by nitroglycerin and its mechanism. The rats were pretreated with ethanol extract of *Ageratina adenophora* (dose: 21.05g/kgbw), and the rats were pretreated by intragastric administration for 7 days. After the last administration, 30 minutes, the rats were induced with nitroglycerin (dose: 10mg/kg). Headache symptoms. Detect the behavioral indicators of rats by recording the times of scratching their heads and climbing their cages, and determine the levels of nitric oxide (NO) in serum of rats by enzyme-linked immunosorbent assay; and the content of calcitonin gene-related peptide (CGRP) and endothelin (ET) in plasma and the content of serotonin (5-HT) and norepinephrine (NE) in the brainstem. The results showed that the ethanol extract of *Ageratina adenophora* significantly reduced the number of head scratching and cage climbing in migraine rats ($P<0.01$), and significantly reduced the levels of NO ($P<0.05$) in serum and CGRP and ET in plasma ($P<0.01$). Increase the content of 5-HT and NE in the brainstem of rats ($P<0.01$). Conclusion: The ethanol extract of *Ageratina adenophora* reduces the damage caused by nitroglycerin and protects the migraine rat model.

***Keywords****: Ageratina adenophora, Alcohol extract, Nitroglycerin, Migraine, Analgesic.*

## I. INTRODUCTION

Migraine is a disease that can often be seen in daily life. It is characterized by severe unilateral throbbing headache, which is aggravated by physical activity. Other symptoms of migraine include nausea, vomiting, light and sound sensitive [1-2]. As a common brain disease, more than 20% of people in the world are affected by migraine at some stage of their lives. The World Health Organization announced in 2015 that migraine is the third most common disease in humans' daily lives. Ranked sixth in the world's diseases that can cause disability [3-4]. At present, migraine treatment drugs mainly include triptans and serotonin receptor antagonists. Although these drugs can treat migraine well, these drugs can bring a series of side effects to the health of the human body. Natural medicines for migraines provide the basis.

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*Ageratina ad*enophora (AA) belongs to the order Chrysanthemum, Compositae, and *Adenophora* is a perennial herb or semi-shrub-like plant [5]. It is an invasive species that grows very vigorously and well, and spreads very fast. It has a huge impact on the production of agriculture, animal husbandry and forestry. In recent years, studies have shown that it has analgesic, anti-inflammatory, hemostatic, anti-tumor, Antibacterial, antiviral, anti-oxidant, antipyretic, wound healing and other pharmacological activities [6-9].

This study aims to further confirm the analgesic effect of *Ageratina adenophora*, provide a certain research value for the development and utilization of *Ageratina adenophora* in biomedicine, and provide a new treatment method and idea for the drug research and treatment of migraine.

## II. EXPERIMENTAL MATERIALS

### 2.1 Experimental Animals

Select SPF-grade male SD rats of 4-6 weeks old and weighing 180g±20g. Purchased from Beijing Huafukang Biotechnology Co., Ltd. (license number: SCXK (Jing) 2019-0008), all animal care and experimental research are carried out in strict accordance with the "Guidelines for the Care and Use of Laboratory Animals" and approved by Yunnan University of Traditional Chinese Medicine. The ethics committee approved (SYXKK20170005).

### 2.2 Experimental Medicinal Materials and Reagents

*Ageratina adenophora* was collected in Kunming, Yunnan Province in August 2019; 95% ethanol was purchased from Tianjin Zhiyuan Chemical Reagent Co., Ltd.; sodium carboxymethyl cellulose was purchased from Renqiu Renxing Chemical Co., Ltd.; nitroglycerin was purchased from Beijing Yi Min Pharmaceutical Co., Ltd.; Aspirin enteric-coated tablets were purchased from Nanjing Baijingyu Pharmaceutical Co., Ltd.; NO (MM-0889R1), CGRP (MM-0652R1), ET (MM-0634R1), 5-HT (MM-0981R2), NE (MM-20302R2) was purchased from an enzyme-linked immunosorbent assay (ELISA) kit from Jiangsu Enzyme Biotechnology Co., Ltd. (Jiangsu, China).

### 2.3 Experimental Instruments

The ultrasonic cleaning instrument (sb-1500dt) was purchased from Ningbo Xinzhi Biotechnology Co., Ltd; The circulating water vacuum pump (shz-d III) was purchased from Gongyi Yuhua Instrument Co., Ltd; Rotary evaporator (rv8032014) was purchased from Eka, Germany; The ultra-low temperature refrigerator (forma907) was purchased from thermo in the United States.

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## III. EXPERIMENTAL METHOD

### 3.1 Preparation of Ethanol Extract of *Ageratina adenophora* (AAEE)

Wash and dry the collected fresh *Ageratina adenophor*a leaves. Weigh 500g into a tissue masher and mash it. Use 2500ml of 95% ethanol for ultrasonic extraction for 30 minutes. Collect the filtrate. After repeated extraction three times, The collected filtrate was concentrated with a rotary evaporator under reduced pressure until the filtrate was concentrated to a paste and the weight did not change, the extract was collected and weighed, and the extraction rate was calculated.

### 3.2 Drug Preparation

Preparation of 1% sodium carboxymethylcellulose: accurately weigh 1g sodium carboxymethylcellulose into a beaker, add 100ml of distilled water and stir and dissolve under heating until the sodium carboxymethylcellulose is completely dissolved After that, the bottle is cooled and labeled and stored at 4°C for later use; aspirin solution preparation: accurately weigh 5g aspirin and dissolve in 10ml saline to prepare a solution with a concentration of 500mg/ml; *Ageratina adenophora* alcohol extract configuration: prepare to weigh 50g *Ageratina adenophor*a extract was dissolved in 10ml of 1% sodium carboxymethylcellulose to prepare a solution with a concentration of 5000mg/ml for later use.

### 3.3 Animal Model Establishment and Treatment

After the SD male rats were appropriately fed in the laboratory for one week, they were grouped by a random number table method and divided into 4 groups, namely the blank group, the model group, the positive control group (aspirin treatment group), and the treatment group. Group (*Ageratina adenophora* alcohol extract treatment group), each group has 10 animals, a total of 40 animals. The rats in the blank group and the model group were given 1ml of normal saline for 7 consecutive days; the rats in the positive control group were given aspirin (dose: 0.23g/kg) for 7 consecutive days, and the rats in the treatment group were given *Ageratina adenophora* for 7 consecutive days. Alcohol extract (dose: 21.05g/kg). Except for the blank group, rats in the other groups were injected subcutaneously with nitroglycerin (GTN) (dose: 10 mg/kg) into the right shoulder of each group of rats 30 minutes after the last administration to induce migraine models.

### 3.4 Behavioral Observation

Rats suffering from migraine will scratch their heads and climb cages more frequently. Start timing when the model is built, and take half an hour as an observation time node, and observe a total of 3 hours. Record the number of times the rat appeared to touch the head with the forelimbs and stand on the edge of the squirrel cage during each time node. The rat started to record at least 5 times when the rat appeared to touch the head with the forelimbs continuously in a time node.

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3.5 Sample Collection

After the migraine model was established 4h, samples were collected. Each rat was anesthetized by intraperitoneal injection of 10% chloral hydrate (dose: 10ml/kg). After anesthesia, the rats were dissected and two blood samples were taken from the heart with a syringe, one was put into 7.5% EDTA-2Na In the treated centrifuge tube, after standing for 30 minutes, centrifuge at 3000r/min for 10 minutes at 4°C, take the supernatant and put it in the EP tube, which is the plasma; put another blood sample in the centrifuge tube, and let it stand for 30 minutes. Centrifuge at 3000r/min for 10 minutes at 4°C, take the supernatant and put it in an EP tube, which is the serum, freeze it in liquid nitrogen for 10 minutes and store it at -80°C. After the blood sample is taken, the brain is quickly taken, the brainstem is separated, washed with normal saline, and then placed in an EP tube, first frozen in liquid nitrogen for 10 minutes, and then frozen at -80°C.

3.6 NO in Serum; Determination of CGRP, ET in Plasma and 5-HT and NE in Brainstem

Enzyme-linked immunosorbent assay (ELISA) was used to determine the content of NO in serum, the content of ET and CGRP in plasma, and the content of 5-HT and NE in the brain stem. The detection of each indicator is strictly in accordance with the corresponding method of using the kit.

3.7 Statistical Analysis

All experimental data results are expressed as mean±standard deviation (mean±△S). The experimental data were analyzed by SPSS 26.0 software, and the differences between the groups were compared by unpaired t-test. P<0.05 indicates that the differences are statistically significant. Use Graphpad Prim8.0.2 software to draw experimental results.

## IV. RESULT

4.1 The Ethanol Extract of *Ageratina adenophora* Reduced the Frequency of Head Scratching and Cage Climbing in GTN-Induced Migraine Rats

During the observation period after GTN was given to the rats, the rats in the model group, positive control group and treatment group all had different degrees of head scratching and cage climbing. The analysis in Table I. shows that compared with the model group, the number of head scratching of rats treated with ethanol extract of *Ageratina adenophor*a and aspirin has been significantly reduced, and the difference is significant ($P$<0.01), indicating that *Ageratina adenophora* the alcohol extract can reduce the number of head scratching in migraine rats. The analysis in Table II. shows that compared with the model group, rats treated with *Ageratina adenophora* alcohol extract and aspirin had a significant reduction in the number of cage climbing after 90 minutes of observation, and the difference was significant ($P$<0.01), indicating that the ethanol extract of *Ageratina adenophora* can reduce the number of cage climbing of migraine rats, and it is inferred that the ethanol extract of *Ageratina adenophor*a can reduce the pain

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caused by migraine in rats.

**TABLE I. Effects of extracts on the number of head scratching in rats at different time**

| Group | Period (min) | | | | | |
|---|---|---|---|---|---|---|
| | 0-30 | 30-60 | 60-90 | 90-120 | 120-150 | 150-180 |
| Control | 2.00±2.16 | 2.00±2.16 | 1.00±1.41 | 3.00±2.16 | 1.00±1.15 | 2.50±1.91 |
| Model | 20.50±4.32$^{\#\#}$ | 20.50±4.32$^{\#\#}$ | 38.00±2.3$^{\#\#}$ | 22.33±2.7$^{\#\#}$ | 19.00±3.35$^{\#}$ | 34.00±3.2$^{\#\#}$ |
| Positive control | 9.67±1.51$^{**}$ | 4.83±2.71$^{**}$ | 2.83±1.17$^{**}$ | 2.17±3.13$^{**}$ | 5.67±1.37$^{**}$ | 5.33±1.03$^{**}$ |
| AAEE | 26.83±17.63 | 13.67±9.58$^{*}$ | 11.50±4.27$^{*}$ | 7.83±7.70$^{**}$ | 11.50±4.56$^{*}$ | 5.33±1.66$^{**}$ |

Note: # it indicates that there is significant difference compared with the Control group ($P$ < 0.05); ## It indicates that there is a very significant difference compared with the Contro group ($P$ < 0.01); * There was significant difference compared with the model group ($P$ < 0.05); ** It indicates that there is a very significant difference compared with the model group ($P$ < 0.01).

**TABLE II. Effects of extracts on the number of climbing cage in rats at different time**

| Group | Period (min) | | | | | |
|---|---|---|---|---|---|---|
| | 0-30 | 30-60 | 60-90 | 90-120 | 120-150 | 150-180 |
| Control | 2.75±2.22 | 3.00±0.82 | 2.25±1.89 | 2.50±0.58 | 0.50±0.58 | 1.50±2.38 |
| Model | 18.83±2.40$^{\#\#}$ | 27.17±2.23$^{\#\#}$ | 12.00±0.8$^{\#\#}$ | 19.17±4.0$^{\#\#}$ | 16.17±3.54$^{\#\#}$ | 18.17±2.93$^{\#\#}$ |
| Positive control | 9.67±2.34 | 6.67±1.86 | 6.00±1.67 | 5.00±1.79$^{**}$ | 2.17±0.75$^{**}$ | 3.00±2.76$^{**}$ |
| AAEE | 15.33±2.25 | 7.00±2.53$^{**}$ | 10.83±1.60 | 7.83±2.32$^{**}$ | 9.00±3.58$^{*}$ | 1.50±2.35$^{**}$ |

Note: # It indicates that there is significant difference compared with the Control group ($P$ < 0.05); ## It indicates that there is a very significant difference compared with the Control group ($P$ < 0.01); * There was significant difference compared with the model group ($P$ < 0.05); ** It indicates that there is a very significant difference compared with the model group ($P$ < 0.01).

4.2 The Alcohol Extract of *Ageratina adenophor*a Reduced the Serum NO Level of Rats.

Figure 1 is the determination of the content of no in rat serum. It can be seen from the figure that the content of no in rat serum injected with GTN increased significantly. Compared with the blank group, there was a very significant difference in the model group ($P$<0.01); After treatment with alcohol extract of *Ageratina adenophora* and aspirin, the content of no in serum of rats decreased significantly, which was significantly different from that of model group ($P$<0.05).

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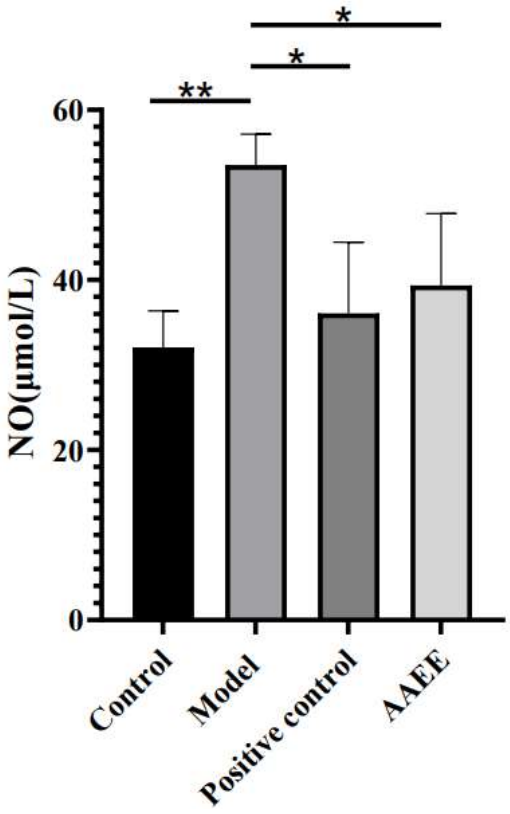


Fig 1: Effects of extracts on the contents of serum NO in rats

4.3 The Ethanol Extract of *Ageratina Adenophora* Reduced the Plasma CGRP and ET Levels in Rats.

It can be seen from Table III. that the CGRP and ET levels in the GTN-induced migraine rat model were significantly decreased and increased, compared with the blank There is a significant difference between the two groups ($P$<0.01). After treatment with the ethanol extract of *Ageratina adenophora*, the levels of CGRP and ET in the plasma of rats were significantly reduced ($P$<0.01), and the reduction level was equivalent to that of the aspirin treatment group. The ethanol extract of *Ageratina adenophora* can play a role in the treatment of migraine by inhibiting the content of plasma CGRP and ET.

4.4 The Ethanol Extract of *Ageratina Adenophora* Improves the Content of 5-HT and NE in the Brainstem of Rats.

By measuring the content of 5-HT and NE in the brainstem of rats, it can be seen from Table IV. that the GTN-induced migraine rat model the content of 5-HT and NE was significantly reduced, and there was a significant difference compared with the blank group ($P$<0.01). After treatment with the ethanol extract of *Ageratina adenophora*, the levels of 5-HT and NE in the brainstem of rats were significantly restored, and there was a significant difference compared with the model group ($P$<0.05).

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**TABLE III. Plasma CGRP and ET contents of rats in each group**

| Group | Dose (g/kg) | CGRP (ng/L) | ET (ng/L） |
|---|---|---|---|
| Control | - | 37.03±2.98 | 198.44±3.20 |
| Model | - | 64.43±1.20## | 485.12±3.03## |
| Positive control | 0.23 | 47.11±4.49** | 379.95±1.87** |
| AAEE | 21.05 | 42.33±1.72** | 397.43±3.96** |

Note: ## indicates a very significant difference compared with the Control group ($P$<0.01); ** indicates a very significant difference compared with the model group ($P$<0.01).

**TABLE IV. Effects of extracts on contents of 5-HT and NE in brain stem of rats**

| Group | Dose (g/kg) | 5-HT (ng/L) | NE (pg/ml) |
|---|---|---|---|
| Control | - | 473.83±2.55 | 276.32±2.36 |
| Model | - | 301.14±2.99## | 200.25±12.15## |
| Positive control | 0.23 | 407.58±1.55** | 235.60±11.06* |
| AAEE | 21.05 | 356.09±5.62* | 219.94±5.10* |

Note: ## indicates a very significant difference compared with the Control group ($P$<0.01); *Indicates that there is a significant difference compared with the model group (P<0.05); ** indicates a very significant difference compared with the model group ($P$<0.01).

## V. DISCUSSION

As a disease that often occurs in people's daily life and is difficult to be completely cured, migraine is extremely harmful to people's lives. Due to the complexity of migraine, there are many complications in clinical manifestations, and its pathogenesis has not been fully elucidated so far, which has brought great difficulties to the development of therapeutic drugs.

In recent years, there are three main viewpoints on the pathogenesis of migraine that have been generally recognized, including the trigeminal nerve-vascular reflex theory, the vascular origin theory, and the neurogenic theory [10]. The trigeminal nerve is the key mechanism for the regulation of intracranial and extracranial blood vessels and the activation of pain stimulation pathways. Local vasoactive substances 5-HT (5-hydeoxyteyptamine, serotonin), CGRP (Calcitionin rene-related peptide, calcitonin) Gene-related peptides), NO (Nitric oxide), ET (Endothelin), NE (norepinephrine), etc. play an important role in reducing pain threshold and increasing pain sensitivity [11-15]. 5-HT is a neurotransmitter as well as a humoral transmitter. It is widely distributed in the local nervous system, cardiovascular tissues, blood cells and central nervous system of the human body. Studies have found that the occurrence of migraine is strongly related to the contraction and relaxation of blood vessels in the human brain. When the blood vessels in the brain dilate, the blood flow becomes smaller and the blood flow rate becomes slower, resulting in a decrease in the concentration of 5-HT, which causes migraine. In addition, the activation of 5-HT receptors on endothelial cells can lead to the production of NO and vasodilation [16-18]. CGRP is a

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neuropeptide substance with multiple functions. Through cAMP (adenosine 3`,5`-cyclicmonophos phate, 3,5`-cyclic adenosine monophosphate) pathway, the NO content in the cell is increased, and the prostacyclin in the body is affected. The effect of CGRP, by acting on the cAMW-PKA pathway, then leads to vasodilation in the human body [19-20]. NO is a small molecule substance that exists in various tissues and organs of the human body. It has protective effects such as expanding blood vessels and improving local tissue blood supply. It regulates the sensitivity of the trigeminal nerve vascular system, stimulates the trigeminal nerve vascular system, and makes the trigeminal nerve The nitric oxide synthase of the nucleus is excited, thereby increasing the excitability of the central nervous system, which plays a key role in the onset of migraine [21]. NE can inhibit the propagation of gray matter cortical diffusion signals and play an analgesic effect [22]. ET participates in the regulation of cerebral vascular tone by constricting blood vessels, increasing the permeability of cerebral microvasculature, causing protein extravasation, activating inflammatory cells, and causing inflammation [23-24].

Nitroglycerin (NTG), as a nitric oxide NO donor, can induce neurogenic inflammation by activating trigeminal nerve endings and release CGRP to induce neurogenic inflammation and cause migraine. It can induce hyperalgesia, behavioral symptoms, and pathophysiological changes in rats. Migraine attacks have a certain similarity, so they are widely used in the establishment of migraine animal models [25-26].

This study found that the ethanol extract of *Ageratina adenophora* can alleviate the behavioral symptoms of migraine head scratching and cage climbing, and can improve the changes in serum NO, plasma CGRP, ET, and brain stem 5-HT, NE content in rats, which preliminarily confirms Eupatorium Ethanol extract has certain anti-inflammatory and analgesic effects on migraine rat models. However, the material basis for the anti-inflammatory and analgesic effects of *Ageratina adenophora* ethanol extract is still unclear, and its mechanism of action still needs to be further explored.

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