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Original Article

A comparative analysis of the anti-inflammatory effects of *Hyssopus cuspidatus* Boriss. essential oil and aspirin on chronic inflammation models in mice

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Abstract: *Background: Hyusopus cuspidatus* Boriss. has been widely used in traditional Chinese medicine formulas to relieve sputum, spasms, dilatation of peripheral blood vessels, and for its anti-inflammatory effects. *Objective:* The aim of this study was to explore the anti-inflammatory properties of *Hyusopus cuspidatus* Boriss. essential oil (HEO) and systematically compare its anti-inflammatory effects with aspirin. *Methods:* Chronic inflammatory model mice were constructed using cotton ball-induced granuloma formation, and then aspirin and two doses of HEO were administered orally, followed by changes in body weight. The drug was used for 7 days, and the oxidative stress index and the inflammation-related factor in the serum of each experimental group model mouse were detected by a kit, and the weight of the granuloma of each group was extracted, weighed and counted. *Results*: The results showed that 0.4 ml/kg of HEO and aspirin significantly inhibited cotton ball-induced granuloma formation and had a good anti-inflammatory effect. Moreover, the anti-inflammatory effect of 0.4 ml/kg HEO is more significant than that of aspirin. In addition, analysis of inflammation-related indicators showed that HEO significantly reduced the MDA and NO levels, and inhibited the production of TNF-α, IL-1β, IL-6 and PGE2, thereby slowing the progression of inflammation. *Conclusion*: the *Hyusopus cuspidatus* Boriss. essential oil has an anti-inflammatory pharmacological function and works by decreasing the concentrations of NO and MDA and inhibiting the expressive levels of IL-1, TNF-α and PGE2 in serum.

Keywords: *Hyssopus cuspidatus* Boriss. essential oil, anti-inflammatory, inflammatory cytokine, inflammation model

Introduction

A traditional Chinese medicine formula is composed of two or more traditional Chinese medicine ingredients and plays an important role in China's thousands of years of health protection and disease control [1]. Moreover, such formulas have shown excellent preventive and therapeutic effects in long-term human clinical trials and have certain effects in all aspects of disease [2]. For example, studies have shown that the Chinese medicine Fangjing decoction can reduce the apoptosis of hippocampal neurons by inhibiting the AKT/mTOR pathway, thereby alleviating the occurrence of brain damage [3]. Puerarin can exert neuroprotective effects by activating the Akt signaling pathway or by increasing the expression of brain-derived neurotrophic factor (BDNF) [4]. In addition, there are many traditional Chinese medicine preparations that can exert anti-inflammatory effects. Loganin is an iridoid glycoside extracted from the Chinese herb hawthorn, which has the effects of inhibiting inflammation and improving memory and can be employed by using TLR4/TRAF6/inactivation of the NF-κB axis, which attenuates the Aβ-induced BV-2 microglial inflammatory response [5]. Qu Yujie Tang (QYJD) has been experimentally proven to inhibit inflammation and anti-oxidative stress in a dextran sodium sulfate-induced colitis mouse model, and QYJD has been made into a commercial drug for clinical application [6]. In addition, Pingchuanning decoction is an effective Chinese medicine preparation for relieving the asthmatic inflammatory response, which inhib-

its autophagy through the PI3K/Akt/mTOR signaling pathway, thereby exerting therapeutic effects [7]. Another traditional Chinese medicine, tanshinone (TanIIA), can affect macrophage polarization and reduce inflammation by improving mitochondrial function and regulating the TLR4-HMGB1/CEBP-β pathway. And it was observed in RAW264.7 cells incubated with LPS that TanIIA can effectively inhibit the expression of miR-155 [8]. In particular, *Hyssopus cuspidatus* Boriss. has medicinal value in traditional Iranian medicine or Chinese Xinjiang Uyghur medicine, and is used as a traditional Chinese medicine for treating cough, asthma, bronchitis, trauma and rheumatism [9-11]. The main distribution of *Hyssopus cuspidatus* Boriss. among the 15 species of vanilla (Lamiaceae) is from the Mediterranean Region to Central Asia, and China's *Hyssopus cuspidatus* Boriss. and *Hyssopus latilabiatus* are the only two species of the genus *Hyssop* in northern Xinjiang [12]. The extract of *Hyssopus cuspidatus* Boriss. has antibacterial properties. In addition, it has antioxidant, expectorant, antitussive, and hypoglycemic properties, and it is known for inhibiting airway inflammation in the body [13, 14]. In this study, the extract *Hyssopus cuspidatus* Boriss. essential oil (HEO) has the effect of soothing smooth muscle and also exerts anti-inflammatory effects in xylene-induced ear edema [15-17]. Currently, the most widely used drug for the inhibition of inflammation is aspirin, so it has been used as a positive control drug in studies of various disease models [18, 19].

On the one hand, the most concerning thing about inflammatory diseases is the imbalance of cytokines, especially the abnormalities of the inflammatory factors, such as the interleukin family, the transforming growth factor family, and the interferon family proteins [20]. These cytokines trigger physiological changes, development, and the metabolism of immune homeostasis, hematopoiesis, and inflammation [21]. Among them, IL-1 is a multifunctional pro-inflammatory cytokine, which can be produced by B lymphocytes, epithelial cells and natural killer (NK) cells, and transmitted to the site of inflammation to play a role [22, 23]. Its ligand IL-1β promotes the apoptosis of glioma cells by inhibiting the production of hypoxia-inducible factor 1 (HIF-1) and adrenomedullin [24]. IL-6 is a potent inducer of local and systemic inflammation and plays a key role in the acute phase response. Its activation is linked to the soluble IL-6 receptor (SIL-6R), which plays a role in dimerization in the presence of gp130 and initiates intracellular signaling [25, 26]. IL-6 can induce vascular overgrowth, leading to increased vascular proliferation and vascular permeability, is a pathological feature of inflammatory lesions, and is common in synovial tissue such as rheumatoid arthritis (RA) or synovitis. Edema [27]. In addition, TNF-[alpha] binds to serum soluble TNF receptors 1 and 2 (human sTNFRI and 2), thereby initiating pro-inflammatory signaling. It exerts its pleiotropic effects by inducing the expression of adhesion molecules, fibroblast proliferation, procoagulant factors, and cytotoxicity, apoptosis, and the onset of acute phase responses [28]. It also has the ability to increase IL-1β, IL-6, IL adverbial clause-33 production, and to modulate ST2 epithelial cell proliferation [29, 30]. Prostaglandin E2 (PGE2) is a helper inflammatory mediator that elicits a wide range of biological effects associated with inflammation. It also plays a variety of roles in biological processes such as cell proliferation, apoptosis, angiogenesis, inflammation and immune surveillance [31]. In the initial phase of the inflammatory response, PGE 2 and related prostaglandins such as PGI 2 act as vasodilators to promote the recruitment of large numbers of neutrophils, macrophages and mast cells in the blood, resulting in swelling, infection, or tissue damage, as well as edema [32]. On the other hand, malondialdehyde (MDA) is a peroxidation product in which oxygen radicals interact with biofilm lipids to reflect the degree of lipid peroxidation in the body. It has been reported that the lack of mda-9/syntenin expression in the host lung affects the local inflammatory network and decreases the levels of pro-inflammatory cytokines such as IL-6 and IL-17A [33]. Nitric oxide (NO) is a highly reactive free radical produced by the reaction of intracellular nitric oxide synthase (NOS) with arginine and oxygen [34]. It can regulate the signaling of a variety of physiological and pathological processes, and in the absence of oxygen and oxidative stress, it induces inflammatory cells to synthesize iNOS and promote inflammation [35, 36].

In this study, a mouse model of cotton ball-induced granuloma was first constructed, and then the inhibitory effect of HEO on the chronic

inflammation model was analyzed. Among them, we measured the change in body weight of the model mice after administration. We also measured the levels of inflammatory factors in the serum of each group of mice, including tumor necrosis factor-α (TNF-α), interleukin -(IL-1) 1β and IL-6, prostaglandin E2 (PGE2). We also measured nitric oxide (NO) and assessed oxidative stress by quantifying malondialdehyde (MDA). The results indicate that HEO has potent anti-inflammatory activity in our chronic inflammation model.

Material and method

Plant material

In July 2014, the whole herb of *Hyssopus cuspidatus* Boriss. was collected from the Altay region of the Xinjiang Uygur Autonomous Region in China and was certified by Zhao Feicui, pharmacist of the Department of Pharmacy, Affiliated Hospital of Xinjiang Medical University.

Chemicals

Aspirin enteric tablets were purchased from Bayer Schering Pharma (Germany) and MDA kits were purchased from Nanjing Institute of Bioengineering (China). ELISA kits for TNF-α, IL-1β, and IL-6 were purchased from Wuhan Colorful Biotechnology Co., Ltd. (China); N-naphthalene/triethylamine hydrochloride and aminobenzenesulfonic acid was obtained from Sigma Aldrich (Shanghai) Trading Co., Ltd. All the other reagents we used are of the highest commercial grade.

Animal

In this study, we used a total of 45 male Kunming mice weighing approximately 18-22 grams each, which were purchased from the Xinjiang Uygur Autonomous Region Centers for Disease Control and Prevention. The animals were maintained at a temperature of 25 ± 2°C and a relative humidity of 40-70% prior to the experiment. These animals have free access to food and water. The animal experiment program was approved by the Animal Ethics Committee of First Affiliated Hospital of Xinjiang Medical University and conformed to the National Guide for the Use of Laboratory Animal Care and Research. All experiments were conducted with the permission of the Chinese government.

Preparation of HEO

The whole herb of *Hyssopus cuspidatus* Boriss. is dried in the shade. Then, according to the method of "Chinese Pharmacopoeia" (No. 4, 2015) [37], the dried material is simply cut into segments and the essential oil is extracted. HEO (yield: 0.18%) was stored in a closed, low temperature environment and stored in the animals tested.

Cotton granule-induced mouse granuloma

The inguinal region of each mouse was subcutaneously implanted into a sterile cotton granule weighing 5 ± 0.5 mg, one on each side, under ether anesthesia according to the method of Rai et al. [38]. The mice were randomly divided into four groups. Animal positive drug groups were treated with aspirin at a dose of 200 mg/kg. The same volume of physiological saline was administered to the model group mice. Two mice received HEO 0.2 mL/kg and HEO 0.4 mL/kg for 7 days by oral gavage. After the last administration, cotton balls with granuloma tissue were removed and dried to a constant weight at 55°C. The serum was separated and stored at -20°C to measure NO, MDA, IL-6, IL-1β, TNF-α, and PGE2. The effect of the drug on chronic inflammation was determined by comparing the results obtained by the test group with the results of the control group.

Determination of serum IL-6, IL-1β and TNF-α levels by enzyme-linked immunosorbent assay (ELISA)

The levels of IL-6, IL-1β, and TNF-α were measured according to the modified method of Daull et al. [39]. Blood samples were taken from the decapitated mice, centrifuged at 4°C using a refrigerated centrifuge, and the serum samples were analyzed by ELISA to evaluate the levels of IL-6, IL-1β, and TNF-α.

Measurement of serum MDA content

The MDA content was determined using the thiobarbituric acid (TBA) method according to Park et al. [40]. Briefly, MDA reacts with TBA at acidic elevated temperatures and forms a red complex MDA-TBA adduct. The absorbance of the MDA-TBA adduct was determined at 535 nm.

Table 1. The effect of HEO on cotton granule formation induced by cotton particles

Group	Dose	n	Weight/mg	Inhibition rate/%
Model	-	8	6.025 ± 1.669	-
Aspirin	200 mg/kg	10	4.489 ± 1.699*	25.50
HEO	0.4 mL/kg	8	4.075 ± 1.892*	32.37
	0.2 mL/kg	8	5.138 ± 0.722	14.73

Notes: compared with the model group,*P<0.05.

Serum NO level determination

Serum was collected and nitrite accumulation was analyzed as an indicator of NO production using Griess reagent. The NO assay was performed as described by Zhang et al. [41]. Briefly, 100 μL of Griess reagent (0.1% naphthylethylenediamine and 1% sulfonamide in a 5% H_3PO_4 solution) was added to an equal volume of supernatant. We incubated the plate for 10 minutes at room temperature and then used sodium nitrite to generate the standards.

Determination of serum PGE2 content in granuloma mice

The level of PGE2 was as described by Zhang Wenke et al. [42]. Briefly, serum samples were added to a second solution of potassium hydroxide in methanol (0.5 mol/L) and then isomerized at 50°C for 20 minutes. After centrifugation at 2,000 × g for 3 minutes at room temperature, the supernatant was removed from the mixture. The absorbance was measured at 278 nm using a spectrophotometer.

Statistical analysis

All results are expressed as the mean ± SD for each group, and the data were statistically evaluated using SPSS 17 software. Differences between groups were compared, and one-way analysis of variance (ANOVA) and Dunnett's *t* test were performed. *P* values less than 0.05 and 0.01 are considered to represent statistical significance.

Results

The effects of HEO on granuloma induced by mouse cotton particles

The planted cotton ball stimulated the mouse to produce an acute inflammatory response, which was subsequently converted into chronic inflammation, thereby constructing a mouse model of cotton granuloma inflammation. When the mouse model was successfully constructed, its body weight increased significantly, and the weight of the granuloma decreased after the drug treatment of the mice. As can be seen from the data in **Table 1**, the weight of the weighed granuloma was significantly reduced in the aspirin and high dose HEO groups compared to the model group mice. There was no statistical significance between the HEO low dose group and the model group. Compared with the 25.50% dose group of aspirin, 0.2 ml/kg and 0.4 ml/kg HEO produced a granuloma weight inhibition rate of 14.75% and 32.27%, respectively. This indicates that the dose of HEO is 0.2 ml/kg, the granuloma weight control of the model mice is weak, and at a dose of 0.4 ml/kg, HEO can effectively control the granuloma weight caused by inflammation. The inhibition rate is higher and better than aspirin.

The effect of HEO on serum malondialdehyde content in mice with granuloma induced by cotton balls

Elevation of MDA impairs the function and structure of the cells, and its determination can indirectly reflect the extent to which the cell is attacked by free radicals. As shown in **Figure 1**, the MDA concentrations in the HEO group and the aspirin group were significantly lower than those in the model group, respectively. However, there was no significant difference between the aspirin group and the HEO group. It can be concluded that HEO can reduce the MDA content in the serum of cotton ball-induced granulomatous inflammation model mice at low doses of 0.2 ml/kg. It shows that HEO is sensitive to the inhibition of oxidative stress, and even a low dose can play a significant role.

The effect of HEO on serum inflammation-related factors in mice with granuloma induced by cotton pill

The level of inflammation-related factors in serum can represent the extent of the inflammatory response that occurs in animal models. We selected a number of pro-inflammatory cytokines to test the effects of HEO on the model's inflammatory response. First, the amount of NO in the serum was measured (**Figure 2**). As

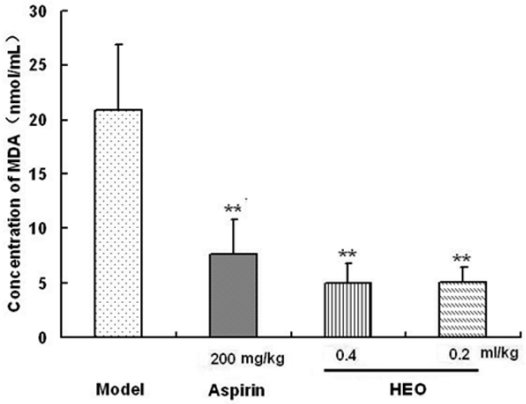

Figure 1. The effect of HEO on the content of MDA in the serum of mice with granuloma induced by cotton balls ($\bar{x}$ ± s, n=6-8, compared to model group, *P<0.05). The abscissa indicates the experimental grouping, in which the diagonal column represents the model group, the black column represents the aspirin group, the vertical column represents the 0.4 ml/kg HEO group, and the horizontal column represents the 0.2 ml/kg HEO group. The ordinate indicates the content of MDA.

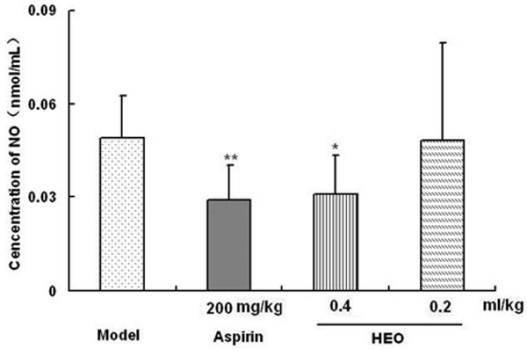

Figure 2. The effect of HEO on the content of NO in the serum of mice with granuloma induced by cotton balls ($\bar{x}$ ± s, n=6-8, compared to model group, *P<0.05; **P<0.01). The abscissa indicates the experimental grouping, in which the diagonal column represents the model group, the black column represents the aspirin group, the vertical column represents the 0.4 ml/kg HEO group, and the horizontal column represents the 0.2 ml/kg HEO group. The ordinate indicates the content of NO.

a result, the serum NO content in the aspirin and HEO high dose group mice was significantly lower than that in the model group. There was no significant difference between the low-dose HEO group and the model group. The data showed that 0.4 ml/kg of HEO significantly reduced the NO content in the serum of the cotton ball-induced granuloma mouse model.

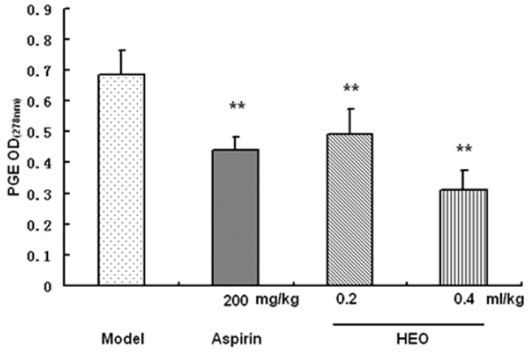

Figure 3. The effect of HEO on the content of PGE2 in serum of mice with granuloma ($\bar{x}$ ± s, n=6-8, compared to model group, *P<0.01). The abscissa indicates the experimental grouping, in which the diagonal column represents the model group, the black column represents the aspirin group, the vertical column represents the 0.4 ml/kg HEO group, and the horizontal column represents the 0.2 ml/kg HEO group. The ordinate indicates the content of PGE2.

HEO did not play a role in reducing serum NO content when the dose was 0.2 ml/kg. There was no difference in NO content between the high dose HEO and the aspirin group.

PGE2 is the most important prostaglandin compound, which plays a regulatory role in the cells, tissues or organs surrounding it after secretion to maintain the homeostasis. Using the kit to detect the level of PGE2 in the serum (**Figure 3**), the serum PGE2 levels were significantly higher in the two doses of HEO (0.2 and 0.4 ml/kg) and 200 mg/kg aspirin after oral administration compared with the model group reduced. And the 0.4 ml/kg of HEO reduced PGE2 content better than the aspirin group.

IL-6 is an initial inflammatory factor that itself can induce many other inflammatory factors to act synergistically to promote an inflammatory response. Measuring IL-6 levels can help better understand the depth of inflammation. The results are shown in **Figure 4**. The level of IL-6 in the serum of the aspirin group was lower than it was in the model group. The level of IL-6 in the high dose HEO group of 0.4 ml/kg was significantly lower than it was in the model group. 0.2 ml/kg. The IL-6 content in the low-dose HEO group was also significantly lower, and there was no significant difference between the low-dose HEO group and the high-dose group. However, two doses of HEO promoted a lower level of IL-6 in the serum than it did in the

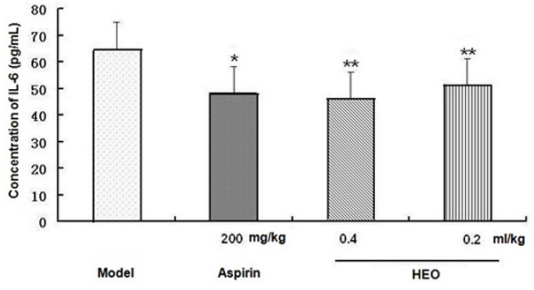

Figure 4. The effect of HEO on the content of IL-6 in the serum of mice with granuloma induced by cotton balls ($\bar{x} \pm s$, n=6-8, compared to model group, $^*P<0.05$; $^{**}P<0.01$). The abscissa indicates the experimental grouping, in which the diagonal column represents the model group, the black column represents the aspirin group, the gray column represents the 0.4 ml/kg HEO group, and the vertical column represents the 0.2 ml/kg HEO group. The ordinate indicates the content of IL-6.

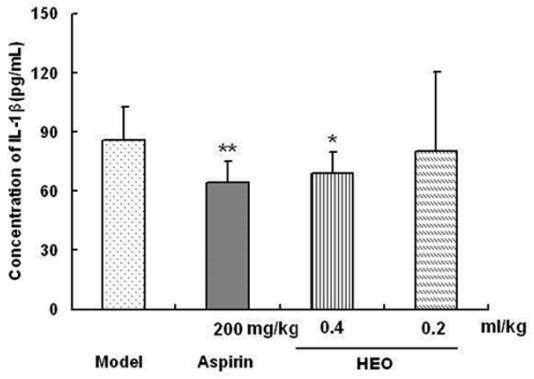

Figure 5. The effect of HEO on the content of IL-1β in the serum of mice with granuloma induced by cotton balls ($\bar{x} \pm s$, n=6-8, compared to model group, $^*P<0.05$; $^{**}P<0.01$). The abscissa indicates the experimental grouping, in which the diagonal column represents the model group, the black column represents the aspirin group, the vertical column represents the 0.4 ml/kg HEO group, and the horizontal column represents the 0.2 ml/kg HEO group. The ordinate indicates the content of IL-1β.

aspirin group, indicating that HEO can better control inflammation. It is also an interleukin family protein, and IL-1β is a multifunctional biomolecule, which is also an important mediator of early inflammatory response. The effect of HEO and aspirin on serum IL-1β in mice with the cotton granule-induced granuloma model is shown in **Figure 5**. Shown. At a dose of 0.4 ml/kg, HEO significantly reduced serum IL-1β levels after oral administration, and aspirin used as a positive control drug had a better effect of

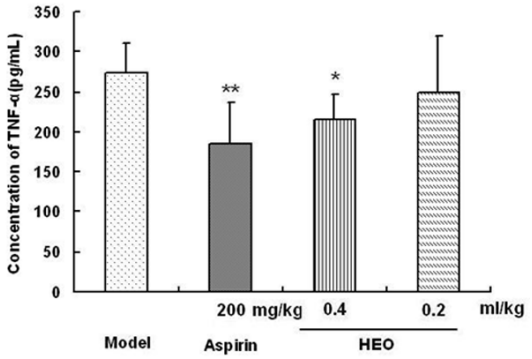

Figure 6. The effect of HEO on the content of TNF-α in the serum of mice with granuloma induced by cotton balls ($\bar{x} \pm s$, n=6-8, Compared with model group, $^*P<0.05$; $^{**}P<0.01$). The abscissa indicates the experimental grouping, in which the diagonal column represents the model group, the black column represents the aspirin group, the vertical column represents the 0.4 ml/kg HEO group, and the horizontal column represents the 0.2 ml/kg HEO group. The ordinate indicates the content of TNF-α.

reducing serum IL-1β content. Serum IL-1β levels were decreased at doses of HEO (0.2 ml/kg), but there was no significant difference between the low-dose HEO group and the model group. This indicates that HEO inhibits IL-1β secretion only at high doses.

The pro-inflammatory cytokine TNF-α is an important initiator of the inflammatory and bactericidal steps. In bacterial pneumonia, macrophage-derived TNF-α is elevated, leading to the recruitment of inflammatory cells at the site of infection to exert anti-infective effects (**Figure 6**), and it can be seen that the TNF-α level of HEO's 0.4 ml/kg high-dose model mice was significantly lower than the levels of the model and the 0.2 ml/kg low-dose HEO group. The level of TNF-α in the aspirin model group was the most significant, and it was significantly lower than the high dose group of HEO. These differences were not statistically significant between the low-dose HEO group and the model group. These results indicate that high doses of HEO can reduce the level of TNF-α in the serum of cotton spheroid-induced granuloma mice, but not as effectively as aspirin.

Discussion

A cotton ball-induced granuloma mouse model is widely used to study the exudation and proliferation stages of chronic inflammation [43,

44]. In a cotton ball-induced granuloma mouse model, cell proliferation accelerates and inflammation becomes chronic in a short time after the onset of acute inflammation. More leukocyte infiltration and fibroblast proliferation occur in the cotton ball-induced chronic inflammation model [45], as cotton balls induce chronic inflammatory processes, i.e., fluid accumulation, monocyte migration and apoptosis will occur in the surrounding tissue of the particles in the granulation tissue that covers the particles [46]. The late stage of granuloma formation is associated with an increased production of NO, PGs, TNF-α, IL-1β, and IL-6, which may in turn aggravate the level of inflammatory response [47]. TNF-α, IL-1β, and IL-6 are involved in cotton-induced neutrophil migration in chronic inflammation of cotton granuloma [48]. In order to investigate the inhibitory effect on chronic inflammation in model mice, we selected two drugs as subjects. Among them, *Hyssopus cuspidatus* Boriss. has many uses in the medicinal system of Xinjiang, including antispasmodic antispasmodic drugs, expectorants, ventilators, peripheral vasodilators, anti-inflammatory drugs, and anti-epileptic drugs, tonics and sweat induction agents [49]. For the treatment of cough, bronchitis, cold, and chronic mucositis and the bronchial system, they are effective [50]. Aspirin is one of the most commonly used drugs in the world [51, 52]. Clinical and epidemiological studies have shown that the use of aspirin varies from 11% to 54% in different populations in different countries [53, 54]. It has been used as an anti-inflammatory analgesic for the past few decades and has a therapeutic effect on many diseases. First, the use of aspirin is associated with a reduced risk of gastric cancer, esophageal cancer, colorectal cancer, pancreatic cancer, ovarian cancer, endometrial cancer, breast cancer, and prostate cancer [55]. Second, aspirin inhibits platelet aggregation by irreversible acetylation of the cyclooxygenase-1 (COX-1) enzyme, leading to an almost complete inhibition of thromboxane, thereby reducing the formation of vascular disease thrombosis [53]. However, aspirin may also cause various adverse side effects, including gastrointestinal bleeding, ulcers, nephrotoxicity and tinnitus [54]. Hypersensitivity reactions may also occur, which are a common clinical syndrome that is exacerbated by the use of drugs, characterized by eosinophils, mast cells, and activated T cells infiltrating the entire respiratory mucosa [55]. Therefore, when using aspirin to relieve or treat some chronic inflammation, the risk of medication is higher.

In the experimental results, both aspirin and HEO show the ability to inhibit the cotton-induced chronic inflammatory response of cotton granuloma. The MDA content is significantly increased at the same time as oxidative damage in cells. In our study, HEO played a better role in suppressing the MDA levels in mouse serum relative to 0.2 ml/kg of aspirin at low doses of 0.2 ml/kg. It indicates that HEO has a strong conditioning effect on oxidative stress in chronic inflammation model mice. In terms of the serum levels of NO, IL-6, IL-1β, and TNFα, although the inhibitory effect of the same dose of HEO was not as obvious as that of aspirin, it showed a significant down-regulation of the inflammatory factors compared to the model group and could trigger inflammation. The initial stages of factor production are regulated. This indicates that HEO has a reconciling effect on the therapeutic effects of chronic inflammation model mice, and it does not merely reduce the inflammatory response, which makes it a better choice in the selection of chronic inflammatory therapeutic drugs.

Taken together, these results indicate that the extract of *Hyssopus cuspidatus* Boriss. has an anti-inflammatory effect. Its anti-inflammatory effects may be related to decreased levels of NO and MDA, as well as the inhibition of the inflammatory factors IL-1β, IL-6, TNF-α, and PGE2. The anti-inflammatory effect of HEO is not weaker than the positive control drug aspirin, so HEO is selective in a way that cannot be ignored, both in terms of efficacy and side effects.

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Disclosure of conflict of interest

None.

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