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ANAGESIC EFFICACY OF DEHEMA PRODUCT IN EXPERIMENTAL ANIMALS

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ABSTRACT

DEHEMA is an herbal product developed from the ancient remedy "Tao Hong Si Wu Tang", clinically prescribed for blood stasis syndrome caused by injury, contusion or surgeries.

Objectives: To evaluate the analgesic effects of DEHEMA in experimental animals.

Methods: The study was conducted using three animal models: hot plate test, Von Frey test and acetic acid-induced writhing test. Mice were divided into five groups and were orally administered: group 1 distilled water; group 2 paracetamol combined with tramadol; groups 3 diclofenac; group 4 DEHEMA high dose of 48mL/kg b.w./day; group 5 DEHEMA low dose of 24mL/kg b.w./day.

Results: The DEHEMA groups showed a tendency in prolonging the heat response time in the hot plate model; prolonging the response time to pain stimuli and increasing force required to elicit pain in Von Frey test; delaying the onset time and reducing the number of writhing in acetic acid-induced writhing model.

Conclusions: This study's findings suggest the potential analgesic effects of DEHEMA in experimental models.

Keywords: DEHEMA, analgesic, hot plate, Von Frey, acetic acid-induced writhing.

1. INTRODUCTION

Traditional medicine has contributed an important part of the healthcare system. Recently, more scientific studies have been conducted to identify the active compounds and investigate the underlying mechanisms of single herbal as well as remedies [1]. The research on medications and products originating from herbal plants has brought evidence for proving the therapeutic efficacy in clinical practice [2].

According to Traditional medicine, pain, swelling and bruises after surgeries are categorized in Blood stasis syndrome [3]. Blood stasis syndrome is a pathological condition of slow, coagulated or stagnant circulation of blood in the body, causing painful sensation [3]. Traditional medicine has a variety of herbals that have blood circulating and blood stasis resolving effects, such as Chuan Xiong, Niu Xi, Dang Gui, Chi Shao, Ru Xiang, Mo Yao... [1,3]

Tao Hong Si Wu Tang, originated from the Yi Zong Jin Jian book written by Wu Qian in 1742, is a primary remedy prescribed for blood stasis syndrome in Traditional medicine. Its therapeutic actions include nourishing the blood, regulating blood circulation and eliminating blood stasis. The common clinical indications of Tao Hong Si Wu Tang are menstrual disorders such as dysmenorrhea, pain and headache due to blood stasis, diabetic neuropathy... [1]. Recent studies have shown the efficacy of Tao Hong Si Wu Tang on reducing symptoms such as pain, swelling and bruises after surgeries [4,5].

DEHEMA is a traditional herbal product, developed from this ancient remedy with the treatment effects of clearing the meridians, removing blood stagnation and relieving pain. DEHEMA consists of Radix Angelica sinensis, Radix Rehmanniae glutinosae, Radix Paeoniae, Rhizoma Ligustici wallichii, Flos Carthami tinctorii (Tao Hong Si Wu tang subtracts Semen Persicae) and Gummi resina Olibanum, Myrrha (additions to enhance the blood stasis elimination). Gummi resina Olibanum and Myrrha have been proved to have significant analgesic and anti-inflammatory properties in many research [1,6].

DEHEMA has shown positive clinical efficacy in treating symptoms on patients after facial plastic surgeries. However, to the best of our knowledge, there hasn't been any study on its analgesic effectiveness in rodent models. Thus, to investigate the scientific evidence of DEHEMA effectiveness, this study was conducted to evaluate its analgesic effect in experimental animals.

2. METHODS

2.1. Research material

The aqueous extract of DEHEMA product used in this study was prepared in 100-mL bottle, manufactured by Medzavy Pharmaceutical Joint Stock Company under the Registration number: 5990/2019/DKSP; lot number: 0224, manufacture date is April 15th, 2024, and expiry date is April 14th, 2027. Research products meet basic standards.

- Ingredients in each 100 mL bottle of DEHEMA: extract from 10g Radix Angelica sinensis, 10g Radix Rehmanniae glutinosae, 8g Radix Paeoniae, 8g Rhizoma Ligustici

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wallichii, 6g Gummi resina Olibanum, 6g Myrrha and 4g Flos Carthami tinctorii; additives includes sugar, preservatives, sodium benzoate, distilled water).

- Effect: Activating blood vessels, dispersing blood stasis, relieving pain.

- Indications: People with swelling, injury, bruising, blood stasis.

2.2. Experimental animals

Healthy white adult Swiss mice, both genders, weighed 25-30g, were provided by the National Institute of Hygiene and Epidemiology. Mice were housed in laboratory conditions for 7 days before the study and during the study with a standard diet and water ad libitum at the Department of Pharmacology – Hanoi Medical University.

2.3. Methods

2.3.1. Hot-plate test

Mice were randomly designated into 5 groups (each group comprised of 10 mice).

- Group 1 (negative control group): Administered distilled water 0.2 ml/10g b.w./day.

- Group 2 (Paracetamol-tramadol group): Administered combination of paracetamol + tramadol at the dose of paracetamol 216.7 mg/kg b.w./day and tramadol 25 mg/kg b.w./day.

- Group 3 (Diclofenac group): Administered diclofenac at the dose of 20 mg/kg b.w./day.

- Group 4 (DEHEMA high dose group): Administered DEHEMA at the dose of 48 mL/kg b.w./day.

- Group 5 (DEHEMA low dose group): Administered DEHEMA at the dose of 24 mL/kg b.w./day.

Mice in all groups were administered water or reagents once a day in the morning with the same volume of 0.2 mL/10g b.w./day in 5 consecutive days.

Mice's response time to heat-induced pain was measured before first dose and one hour after the last dose of water/reagents. Mice were placed on the hot plate (Model DS37, Ugo Basile, Italy) maintained at a constant temperature of 560C by a thermostatic system. Measured the amount of time from when mice placed on the hot plate until mice withdrew or licked their hind paws or jumped. Exclude mice which reacted too quickly (before 8 seconds) or too slowly (after 30 seconds). Compared the response time to heat stimulation inducing pain between before and after taking reagents [2].

2.3.2. Von Frey test

White mice were randomly designated into 5 groups (each group comprised of 10 mice) as in hot plate test.

Mice in each group were given water or reagents with the same volume of 0.2 mL/10g b.w./day, once a day in the morning for 5 consecutive days.

The force required to elicit mice's paws withdrawal response and response time until they withdrew, licked or shook their paws were measured by Ugo Basile's Dynamic Plantar Aesthesiometer 37450, using a Von Frey filament. Comparison was assessed between before the first dose and 1 hour after the last dose [2].

2.3.3. Acetic acid-induced writhing test

White mice were randomly designated into 5 groups (each group comprised of 10 mice) as in hot plate test.

Mice in each group were given water or reagents with the same volume of 0.2 mL/10g b.w./day, once a day in the morning for 5 consecutive days.

One hour after the last dose of reagent, mice were injected intraperitoneally with an acid acetic 1% solution to conduct contractions. The number of mice's writhing was cumulatively counted every 5 minutes until the 30th minute after the acetic acid injection [2].

2.4. DATA ANALYSIS

The data was collected and analyzed using Microsoft Excel version 2010 and SPSS software version 22.0. Paired samples t-test was used for comparison within the group. Student's t-test was used to determine significant differences between two groups. The one-way ANOVA and Bonferroni post-hoc test were used to compare multiple groups. A p value of less than 0.05 was considered as statistically significant.

3. RESEARCH RESULTS

3.1. Hot plate method

Table 1. Effect of DEHEMA on response time to heat stimulation

Research group	Response time (seconds)	
	Before first dose	1 hour after the last dose
Negative control	18.69 ± 5.02	14.55 ± 4.05
Paracetamol + tramadol	15.84 ± 2.88	21.09 ± 5.23*#
Diclofenac	18.80 ± 5.31	14.30 ± 4.72
DEHEMA 48 mL/kg	18.60 ± 5.20	16.39 ± 4.35
DEHEMA 24 mL/kg	17.38 ± 5.16	17.46 ± 4.03

**p < 0.05 compared to before first dose (Paired t-test): #p < 0.05 vs. negative control group (Student's t-test)*

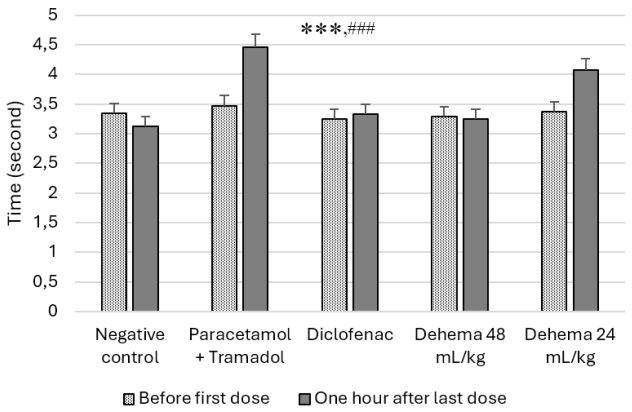
After 5 days, mice taking the combination of paracetamol and tramadol had a significantly longer response time to heat stimulation compared to before first dose and to this of the negative control group ($p<0.05$). Diclofenac has not shown analgesic effect in this study model. DEHEMA at low dose tended to prolong the response time compared to before first dose and negative control group, however the difference was not statistically significant.

3.2. Von Frey test

Table 2. Effect of DEHEMA on force required to elicit pain

Research group	Force required to elicit pain (N)	
	Before first dose	1 hour after the last dose
Negative control	15.51 ± 5.01	14.60 ± 3.46
Paracetamol + tramadol	16.06 ± 2.46	19.10 ± 3.10*,#
Diclofenac	15.11 ± 4.89	15.45 ± 4.46
DEHEMA 48 mL/kg	15.27 ± 4.54	15.11 ± 3.34
DEHEMA 24 mL/kg	15.63 ± 5.19	18.78 ± 5.31

**p<0.05 compared to before first dose (Paired t-test); #p<0.05 compared to the negative control group (Student's t-test);*



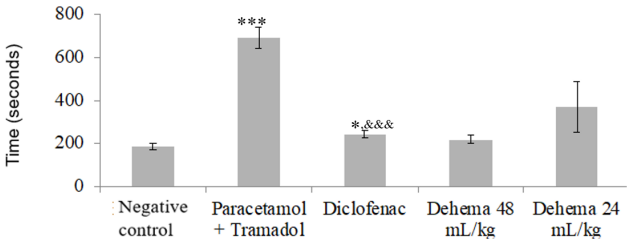
****p<0.001 compared to before first dose (Paired t-test); ###p<0.001 compared to the negative control group (Student's t-test)*

Figure 1. Effect of DEHEMA on response time to Von Frey stimulation

Table 2 and Figure 1 describe the changes in the force required to elicit mice's paws withdrawal and the response time to mechanical stimulation induced by the Von Frey monofilaments before the first dose and after the last dose of water/reagent. In Paracetamol + tramadol group: mice's required force to induce pain and mice response time to filament stimuli significantly increased ($p<0.05$ and $p<0.001$, respectively) when compared to these figures at before first dose and of the negative control group. Diclofenac and DEHEMA groups showed no significant difference in force required and pain response time when compared to before first water/reagent administration and to the negative control group.

3.3. Acetic acid writhing test

The onset time of the first writhing (painful contraction) induced by peritoneal injection of acetic acid solution in each group is shown in Figure 2.



**p<0.05; ***p<0.001 versus negative control group (Student's t-test); &&&p<0.001 versus the combination of paracetamol and tramadol (Student's t-test)*

Figure 2. Effect of DEHEMA on the onset time of writhing

Figure 2 revealed that the combination of paracetamol and tramadol showed a significant prolongation of the onset time of the first writhing in mice injected intraperitoneally with acetic acid solution when compared to the negative control group ($p<0.001$). Diclofenac also showed efficacy in prolonging the onset of writhing compared to the negative control group ($p<0.05$), however this difference was less significant than the difference between group 1 and 2 ($p<0.001$). DEHEMA at the studied doses tended to prolong the onset of writhing, but the differences were not statistically significant.

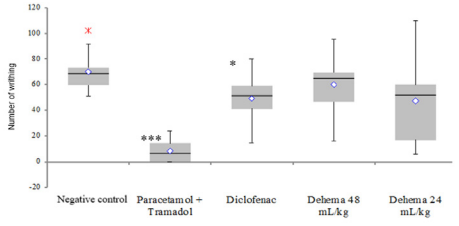
The numbers of writhing every 5-minute intervals within 30 minutes of five groups are shown in Table 3. The paracetamol + tramadol combination significantly reduced the number of writhing compared to the negative control group at all time points ($p<0.001$). Diclofenac tended to reduce the number of writhing compared to the negative control group, with a statistically significant difference in the first 15 minutes after peritoneal injection of acetic acid solution. DEHEMA at both doses showed a tendency to decrease the number of painful cramps compared to the negative control group, but the differences were not statistically significant.

Table 3. Effect of DEHEMA on the number of writhing every 5-minute intervals

Research group	Number of writhing in 30 minutes					
	0-5 minutes	5-10 minutes	10-15 minutes	15-20 minutes	20-25 minutes	25-30 minutes
Negative control	8.90 ± 2.81	17.80 ± 5.31	18.50 ± 5.30	12.00 ± 3.59	7.20 ± 1.99	5.80 ± 1.69
Paracetamol + tramadol	0.00 ± 0.00***	0.57 ± 1.51***	2.14 ± 2.27***	2.29 ± 2.98***	2.57 ± 3.15***	1.86 ± 2.12***
Diclofenac	4.50 ± 4.07*	10.63 ± 5.21*	10.38 ± 5.32**	10.88 ± 5.44	7.13 ± 3.72	5.63 ± 2.33
DEHEMA 48 mL/kg	7.00 ± 4.29	14.60 ± 4.40	13.30 ± 6.53	10.30 ± 3.92	8.20 ± 3.71	6.50 ± 4.70
DEHEMA 24 mL/kg	5.67 ± 4.66	11.67 ± 7.68	9.22 ± 7.34**	8.56 ± 7.14	6.67 ± 5.00	5.67 ± 5.81

**p<0.05; **p<0.01; ***p<0.001 compared to negative control group (Student's t-test)*

Figure 3 represents the total number of writhing of each group counted within 30 minutes. The positive control groups administered analgesics (paracetamol + tramadol group, and diclofenac group) both statistically significantly reduced the total number of contractions compared to the negative control group. DEHEMA at both study dose levels tended to reduce the total number of painful cramps compared to the negative control group, however the differences were not significant ($p>0.05$).



**p<0.05; ***p<0.001 compared to negative control group (Student's t-test)*

Figure 3. Effect of DEHEMA on the number of writhing in 30 minutes

4. DISCUSSION

DEHEMA is a product indicated for people with swelling, bruising, injury or blood statis syndrome according to Traditional medicine. In this study, we evaluated the analgesic effect of DEHEMA product in three models inducing pain by heat stimuli (hot plate test), mechanical stimuli (Von Frey test) and acetic acid solution. These models were used to evaluate peripheral and central analgesic effects [2].

The hot plate test is used to assess centrally mediated analgesic activity by determining the heat threshold in experimental studies on rodents. The heat stimuli were applied to the hind paws and the response time to heat stimuli (response latency) is recorded from beginning to when a nocifensive behavior is observed. Nocifensive behaviors used to mark the time in our study were mice's hind paw withdrawal or licking or jumping, since mice's forepaws are not consistently in contact with the metal surface of the hot plate due to their frequent use in grooming and exploration [2]. The results of the study on the analgesic effect of DEHEMA at 2 doses of 48 mL/kg b.w./day and 24 mL/kg b.w./day revealed that DEHEMA showed a tendency in prolonging the heat response time in the hot plate model.

Von Frey test is one of the methods using mechanical stimuli to induce pain in rodents. This test is used to evaluate both peripheral and central analgesic effects. Rodents are placed individually in small cages with a mesh or barred floor. Monofilaments of increasing forces are applied perpendicularly to mice's hind paws. If a positive response of withdrawing, licking or shaking the paw is recorded, the force of the von Frey filament that elicits this is designated as the mechanical withdrawal threshold [2]. DEHEMA at two studied doses of 48 mL/kg b.w./day and 24 mL/kg b.w./day exhibited a tendency in prolonging the response time to pain stimuli by Von Frey filament and increasing the force required to elicit pain.

The acetic acid-induced writhing test is a chemical method used to induce peripheral origin pain by injecting mice intraperitoneally acetic acid solution. This procedure activates the prostaglandin synthesis which can induce abdominal contractions [2]. Mice in two groups administered DEHEMA at two doses of 48 and 24 mL/kg b.w./day had a slight delay in writhing occurrence and reduce in the number of writhing in this model.

DEHEMA was designed with the herbal formula consisting extract from Radix Angelica sinensis, Radix Rehmanniae glutinosae, Radix Paeoniae, Rhizoma Ligustici wallichii, Gummi resina Olibanum, Myrrha and Flos Carthami tinctorii. This was developed from the Tao Hong Si Wu ancient remedy with additions and subtractions [1].

Chen (2024) evaluated the effect of the decoction of Tao Hong Si Wu tang on the joint rehabilitation process after laparoscopic knee surgery. The results showed that the decoction of Tao Hong Si Wu tang improved blood clotting function, increased the mobility of the knee joint, accelerated the pain relief process and promoted knee joint rehabilitation [4].

Huang (2024) evaluated the effect of the decoction of Tao Hong Si Wu tang on postoperative swelling and pain and inflammatory indicators in elderly patients with fractures. After surgery, the pain scores and limb swelling scores were lower than before surgery. The decoction reduced the inflammatory response, promoted improvement in postoperative pain and swelling, relieved clinical symptoms, and reduced the rate of postoperative complications [5].

The significant analgesic effects of Myrrha have been proved by the pilot study conducted by Germano et al (2017). 95 female and 89 male volunteers (aged 18 to older than 60 years old) experiencing different pain pathologies, (headache, fever-dependent pain, joint pain, muscle aches, lower back pain, and menstrual cramps) were divided into two groups. The experimental group received 1 capsule/day containing either 200 mg or 400 mg of MyrLiq (Myrrha extract) for 20 days, and the placebo group was given the same number of capsules with no MyrLiq. Male volunteers' pain alleviation was obtained with 400 mg of MyrLiq/day for the majority of pain origins. Female volunteers' lower back pain and fever-dependent pain were achieved with only 200 mg of MyrLiq/day [7].

Carthami tinctorii (Safflower) is a useful plant for painful menstrual problems, post-partum hemorrhage, whooping cough and chronic bronchitis, rheumatism and sciatica. The flowers of C. tinctorius are an important medicinal material in prescriptions used for cardiovascular, cerebrovascular and gynecological diseases. In rats, intraperitoneal injection of Safflower Yellow A at doses ranging from 50 to 100 mg/kg showed sustained analgesic effects. Safflower has exhibited central analgesic activity at a dosage of 500 mg/kg, potentially resembling morphine-like effects without the associated side effects. These findings indicate that Flos Carthami tinctorii has analgesic effects [8,9].

5. CONCLUSIONS

The study on DEHEMA at two studied doses of 48 mL/kg b.w./day and 24 mL/kg b.w./day suggests a potential analgesic effect in animal models by a tendency in prolonging the heat response time in the hot plate model; prolonging the response time to pain stimuli and increasing force required to elicit pain in Von Frey model; delaying the onset time and reducing the number of writhing in acetic acid-induced writhing model.

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