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Soft tissue contusion repairing effects of *Hong Yao* with different penetration enhancers

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ABSTRACT

Ethnopharmacological relevance: *Hong Yao* aerosol (HYA) is a new dosage form developed from *Hong Yao*, a traditional Chinese medicine preparation, which has the efficacy of promoting soft tissue contusion repair, anti-inflammation, and analgesia.

Aim: To evaluate the soft tissue contusion repairing, anti-inflammatory and analgesic effects of HYA formulations with different penetration enhancers (PE) and to quantify the transdermal absorption of HYA component.

Materials and methods: Three preparations of HYA with different PEs were made: DMSO preparation (5% DMSO as additional PE), Azone preparation (3% azone as additional PE), and NAPE preparation (no additional PE). Four *in vivo* rodent models were employed to evaluate the pharmacodynamic effects of the HYAs: mouse soft tissue contusion model, rat paw edema model, mouse ear swelling model, and mouse analgesia model of electric-stimulated foot. *In vitro* skin penetration experiment was applied to evaluate the transdermal absorption of HYA components.

Results: All HYA preparations showed effects on soft tissue contusion repairing, anti-inflammation, and analgesia compared with the blank control ($p < 0.05$). There was no significant difference among the three preparations. Pathological variation of mice skin and the pain response time (PRT) reduction phenomena indicated that DMSO preparation induced skin irritation. *In vitro* skin penetration experiment showed no significant difference between DMSO and NAPE on absorption enhancement of ferulic acid from HYA.

Conclusions: NAPE preparation was considered as best and Menthol/borneol (6.3%, W/W, 4:1.75) in HYA might be a good PE combination.

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1. Introduction

A soft tissue injury is the damage of muscles, ligaments and tendons throughout the body. Common soft tissue injuries usually occur from a sprain, strain, a one off blow resulting in a contusion or overuse of a particular part of the body. Soft tissue injuries can result in pain, swelling, bruise, and loss of function (Lovering, 2008). *Hong Yao* is a traditional Chinese medicine (TCM) prescription with the efficacy of promoting soft tissue contusion repair, anti-inflammation, and analgesia. It is composed of Notoginseng Radix, Angelicae Dahuricae Radix, Eupolyphaga Seu Steleophaga, Chuanxiong Rhizoma, Angelicae Sinensis Radix, Carthami Flos, Borneol and Menthol. *Hong Yao* has been used for the treatment

of soft tissue contusion and local bruises, as well as related swelling and pain for hundreds of years (since 1583, *Ching* Dynasty).

Hong Yao aerosol (HYA), developed from the oral *Hong Yao* pill as topical application, has become more acceptable for its better convenience, in which DMSO was used as PE (Li et al., 2000). PE is chemical compound that interact with stratum corneum lipids allowing better penetration of coadministered compounds through this relatively impermeable barrier (Christine and Bozena, 1995). During the clinical use of HYA, skin allergy induced by DMSO was occasionally received as side effect (Ji, 2004; Ma and Zhou, 1998).

In order to solve the clinical problem, we evaluated the pharmacodynamic effect of HYA with different PEs in accordance with its efficacy, meanwhile attended to avoid influence on clinical effectiveness. Considering *Hong Yao* is a complex prescription, *in vivo* rodent models were selected for evaluation and *in vitro* rat skin penetration experiment was applied to quantify the absorption of active component in HYA.

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2. Materials and methods

2.1. Preparation of HYA with different PEs

Six TCMs in HYA were purchased from Bozhou Medical Materials Company and authenticated by Professor Jun Yin in Pharmacognosy Department of Shenyang Pharmaceutical University. Borneol and menthol were purchased from Nantong menthol Industries, Ltd. (Nantong, China) and Guangzhou Baiyunshan Chinese Materia Medica Company (Guangzhou, China) respectively. The original plants or animals of these materials are listed in Table 1 and the voucher specimens numbered from 1001–1008 were deposited in pharmacognosy department of Shenyang pharmaceutical university.

HYA preparations were made by Shenyang Hongyao Pharmaceutical Co. Ltd. (Lot number: 100301). Briefly, the six TCMs were chopped, mixed, and extracted with 90% ethanol for 3 times and condensed in vacuum until the density was 0.85–0.87 (measured at 25 °C). Then borneol and menthol were added into the extract. The excipients including thickener, flavorant, etc. were the same except different PEs shown in Table 2.

Commercial HYA was used as the positive control in our study, because the effect of HYA preparation with new PE should not be worse than the commercial one. Original formula with commonly used PE azone (3%, W/W. Christine and Bozena, 1995; Zhu and Zhou, 2006) and original formula without additional PE (NAPE) were designed and made to compare with the commercial HYA (5% DMSO as PE, W/W).

2.2. Animals and treatments

Four *in vivo* rodent models were employed for pharmacodynamic evaluation: mouse soft tissue contusion model was preferred because its etiopathogenesis and symptom were consistent with human soft tissue injury (Wang et al., 2005; Zhou et al., 1991). Rat paw edema model, mouse ear swelling model, and analgesia model were also employed because they were consistent with the inflammation and pain caused by soft tissue injury (Chen, 1993; Xu and Bian, 2002). According to the SFDA policy, the above four models are enough to assess TCM prescriptions with efficacy of soft tissue contusion repairing, anti-inflammation and analgesia.

Kunming (KM) strain mice (6 weeks) weighing 20 ± 2 g and Wistar rats (6 weeks) weighing 180 ± 20 g were purchased from the Experimental Animal Centre of Shenyang Pharmaceutical University (Shenyang, China). Animals were housed in a room at a temperature of 21–23 °C, a relative humidity of 30–70%, and had free access to food and water. All experimental procedures carried out in this study were

performed in accordance with the Guidelines for the Care and Use of Laboratory Animals of Shenyang Pharmaceutical University. This study was approved by the National and International Ethical Committee.

Animals were randomly divided into four groups: blank control group, DMSO group (positive control), Azone group and NAPE group. Animals in blank control group were wiped with normal saline, while treated groups were sprayed with HYA-5% DMSO, HYA-3% Azone, and HYA-NAPE according to the usage of the commercial HYA.

2.3. Instruments and reagents

Carrageenan was purchased from Sigma Corporation (St. Louis, USA). All the other chemicals were purchased from Yuwang Chemicals Industries, Ltd. (Shenyang, China). Pharmacological and physiological RM6240 BD multi-channel instrument (Number: CD0607, Chengdu Instrument Manufacturing Factory, China) was used in analgesia study. YB-P6 penetration absorption device (Number: 1014, Tianjin Pharmacopeia Standard Instruments Factory, China) was used for *in vitro* penetration absorption study. The HPLC system (Shimadzu Corporation, Japan) consisted of an FCV-10AL pump, an LC-10AT sample processor, and an SPD-10 A UV detector. The chromatography was performed on a 200×4.6 mm² C18 column (Diamonsil, Dikma Technologies Incorporation, 11 Orchard Road, USA).

2.4. Soft tissue contusion in mouse

Mouse soft tissue contusion model is a classical model for evaluation of drugs with the effect on promoting soft tissue injury repair, the presence of ecchymosis and bruise proves the success of modeling (Zhou et al., 1991; Cheng et al., 2007). In our study, 40 KM mice (male and female in half) were shaved on the left part of rear skin 24 h before the administration. Hair removal agent consisted of 2.5 g sodium sulfide, 3.5 g talcum powder, 0.5 g soap powder, adequate amount of water, and corn starch (Lu and Fan, 1965). Soft tissue contusion hitting device was homemade

Table 2
PEs in different HYA formulations.

Formulation number	Formulation abbreviation	Additional penetration enhancer
1	DMSO	5% DMSO
2	Azone	3% azone
3	NAPE	–

Table 1
The composition of HYA formula.

Scientific name	Latin name	Ratio (%)
<i>Panax notoginseng</i> F.H. Chen (Araliaceae)	Notoginseng Radix	41.2
<i>Angelicae dahuricae</i> Benth. et Hook. f. (Umbelliferae)	Angelicae Dahuricae Radix	9.6
<i>Eupolyphaga sinensis</i> Walk. (Eupolyphaga)	Eupolyphaga Seu Steleophaga	9.6
<i>Ligusticum chuanxiong</i> Hort. (Umbelliferae)	Chuanxiong Rhizoma	9.6
<i>Angelica Sinensis</i> Diels. (Umbelliferae)	Angelicae Sinensis Radix	9.6
<i>Carthamus tinctorius</i> L. (Compositae)	Carthami Flos	9.6
Menthol	Menthae Haplocalycis Herba (purity 95–105%)	4.4
Borneol	Synthetic form (purity > 55%)	1.9
Total		100

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