Herbal Pharmacology in Pain Management

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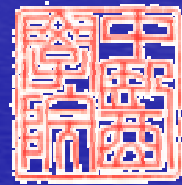
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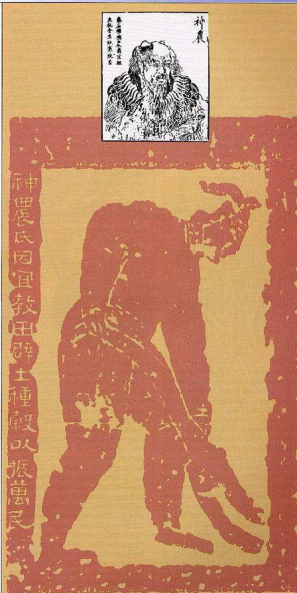
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Contents of the talk

- Chinese Herbal medicine for pain – History and theory
- Treatment of pain with Chinese herbs – some examples
- Pharmacological basis of Chinese herbs for pain
- Is it effective? – systematic review of published literature

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Chinese Herbal medicine for pain – History and theory

- **CM has long been used for pain management.**

The Inner Classic of the Yellow Emperor 黃帝內經
➤*devotes an entire chapter to the studies of pain, 黃帝內經 – 舉痛論 and*
➤*lays the theoretical foundation for the etiology, pathogenesis and treatment strategies for pain.*

# How CM views pain – Basic concepts

Blockage of meridians causes pain; pain is caused by impediment of circulation of qi and blood 不通則痛

Wind, cold, dampness, heat, qi stagnation, blood stasis, Phlegm turbidity can cause blockage of meridian and qi/blood circulation.

Deficiency of vital substances (nutrients) also causes pain 不榮則痛

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Management of pain – CM perspective

- **To expel the pathogenic factors that cause the blockage of meridians.**
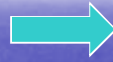
> Expelling wind,
> Dispelling cold,
> Transforming dampness
> Clearing heat,
> Dissolving food stagnation
> Regulating qi stagnation
> Invigorating blood circulation
> Transforming phlegm turbidity.

Pain

> Nourishing yin essence
> Warming yang
> Supplementing qi
> Tonifying blood

To supplement the deficiency of vital substances.

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Chinese herbs with analgesic effects

- **Over 300 Chinese herbs are known to have analgesic effects for various pains.**

- **According to their functions and indications in CM, they are broadly categorized into the following types:**

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- **Exterior-resolving analgesic herbs**解表止痛藥: 白芷 細辛 羌活.
- **Wind-dampness expelling analgesic herbs**祛風濕止痛藥: 威靈仙 獨活 秦艽.
- **Heat-clearing analgesic herbs**清熱止痛藥: 山豆根 射干 馬勃.
- **Blood invigorating & stasis removing analgesic herbs**活血祛瘀止痛藥: 延胡索 乳香 沒藥 三七.
- **Qi-regulating analgesic herbs**行氣止痛藥: 木香 香附 烏藥.
- **Interior-warming analgesic herbs**溫里止痛藥: 高良姜 吳茱萸.
- **Anesthesiac analgesic herbs**麻醉止痛藥: 川烏 草烏 祖師麻 曼陀羅.
- **Other analgesic herbs**其他止痛藥: 罌粟殼.

Routes of administration of CM
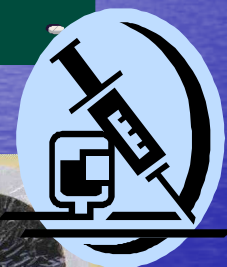
- **Oral (decoction, tincture, pills, tablets, capsules, granule, powder)**
- **Topical (paste, plaster, balm, ointment, spray)**
- **Injection (i.v. and i.m.)**
- **Steaming and bathing.**

Treatment of pain with Chinese herbs – some examples

- **Cai, Y.D. 1995. Treatment of 40 cases of pain conditions with topical application of Bing-Chan tincture.** *Jiangsu Journal of Chinese Medicine 16(8): 44-45.*

Types of pain and baseline data

	Cancer pain	Post-stroke limb pain	Rheumatoid arthritic pain	Soft tissue pain	Osteoarthritic pain	Pain with no clear cause
Treatment group	16	11	6	3	3	1
Control group	12	12	4	5	4	3
Total	28	23	10	8	7	4

Methods:
- Double-blind (patients, researcher blinded)
- Block randomization (quasi-)
- Preparation of Bing-Chan tincture:
- ➤Composition: 冰片 蟾蜍 血竭 紅花 乳香 沒藥 田七. The above materia medica were ground to powders and then soaked in white wine for 7 days. The alcoholic extract was used for treatment.
- Application: the extract was applied 4-5 times daily to the pain area. Other analgesics suspended.
- Duration: 7 days as a course of treatment.
- Control treatment: 紅花 tincture.

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Treatment evaluation:
- VAS (Developed by Zhongshan Hospital, Shanghai Medical University)
- ➤significantly effective 顯效– reduction 40-100;
- ➤effective 有效– reduction 10-40;
- ➤Ineffective 無效 – reduction <10, or need other analgesics;
- ➤worsened 惡化– increase > 20 and require other analgesics.

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Results:

Analgesic effect within 2 h of the treatment with Bing-Chan tincture

	Total patients	Significantly effective	Effective	Ineffective	Worsened	Total effect
Treatment group	40	25	11	4	0	90%
Control	40	5	10	20	5	37.5%

Analgesic effect after 1 week treatment with Bing-Chan tincture

	Total patients	Significantly effective	Effective	Ineffective	Worsened	Total effect
Treatment group	40	12	19	6	3	77.5%
Control	40	0	8	26	6	20%

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Author's conclusions:

- **Bing-Chan tincture is an effective and rapid-acting analgesic preparation.**

- **Acts within 15 min of application and lasts for 3-4 h.**

- **The associated side effect is minimal.**

- **The preparation is not addictive.**

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Pharmacological basis of Chinese herbs for pain

1. *Yan-Hu-Suo* 延胡索 and *l-tetrahydropalmatine (l-THP)* 延胡索乙素

- *Yan-Hu-Suo* 延胡索 is the dried tuber of *Corydalis yanhusuo* W.T. Wang;

- It has the therapeutic functions of invigorating blood circulation and regulating qi movement and stopping pain; and

- Clinically, it is indicated for various pain such as angina, headache, stomachache, hypochondriac pain and dysmenorrhea.

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l-tetrahydropalmatine (l-THP) 延胡索乙素
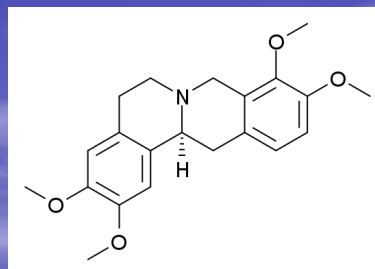
- The main constituent responsible for analgesic action of *Yan-Hu-Suo*.

- Its antinociceptive mechanism involves neither antipyretic nor narcotic pathway.

- Exhibits no affinity for the opiate receptors, but

- Elicits antinociception via antagonistic effect on the D2 dopamine receptors.

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- Commonly used in China as a non-anti-pyretic and non-narcotic analgesic under the trade name of Rotundine 顱通定 for peptic ulcerative pain, migraine, headache, post-partum pain, dysmenorrhea and pain-caused insomnia.
- Can be delivered through oral (60-120 mg, q.i.d) or intramuscular (60 mg) administration.

## 2. *Gao-Wu-Tou* 高鳥頭 and Lappaconitine hydrobromide (LH) 氫溴酸高鳥甲素

高鳥頭

- *Gao-Wu-Tou* 高鳥頭 is the root of *Aconitum sinomoutanum* Nakai.
- It has the therapeutic functions of wind expelling, dampness relieving, blood stasis removing and pain stopping, and
- Is indicated for various pains such as rheumatic and rheumatoid arthritis and cancer pain.

Lappaconitine hydrobromide (LH) 氢溴酸高乌甲素

- is the hydrobromide salt of lappaconitine, a diterpene alkaloid found in *Aconitum sinomoutanum.*
- Was approved in China in 1982 as a non-opioid prescription drug for Three-step Analgesic Ladder for Cancer Treatment (癌症病人三階梯止痛療法).
- Is a non-dependent analgesic.
- Administration routes: epidural, i.v., oral in tablet, or topical in plaster form.
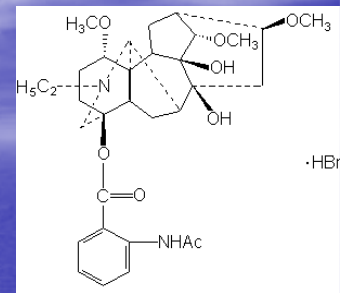
WHO's Pain Relief Ladder
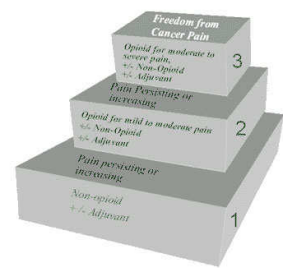
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Lappaconitine hydrobromide (LH) 氢溴酸高乌甲素 (cont'd)

- Possesses potent analgesic effect on cancer pain similar to pethidine with slower but longer-lasting action.
- Has no dependency and withdrawal symptoms and accumulating toxicity.
- Commonly used for mild to moderate cancer pain.
- Or used as adjuvant therapy to reduce the dose of morphine.

LH is also used for:

- Post-operative pain;
- Peptic ulcerative pain;
- Shingle-related neuralgia, especially in elderly patients;
- Arthritic and sciatic pain; and
- Pain of urinary tract syndrome.

Analgesia of Lappaconitine: Mechanisms of action

- General analgesia - Anti-inflammatory effect through inhibition of the production of COX and PGS.
- Central analgesia - achieved through modulating the amount of monoamine transmitters such as 5-HT and noradrenalin in the brain.
- Action sites are similar to those of morphine i.e. periaqueductal gray (PAG) and nucleus raphe magnus (NRM), but via different mediators.
- Is independent of opium receptors.

Is it effective? – systematic review of published literature

Objective:

- To evaluate the effectiveness and safety of Chinese herbal medicine for alleviating cancer pain when compared to placebo or conventional treatment.

Methods:

- systematic review and meta-analysis.

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Inclusion criteria:

Types of studies

- **Randomized controlled trials (RCTs).**

Types of participants

- **Patients with cancer-related pain, which is believed to be directly associated with the development of the cancer.**

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Types of intervention

- **The treatment included Chinese herbal medicine, involving extracts from herbs, single or a mixture of herbal preparations regardless of their compositions, formula forms or administration route, and compared with placebo or conventional treatment.**

- **Those studies on the combination therapy of different approaches of Chinese medicine were excluded.**

Types of outcome measures

- **Pain intensity/pain relief reported by patient;**

- **Analgesic consumption.**

Information sources

English databases

Medline, Embase, and CENTRAL

Chinese databases

CBM and CM-online
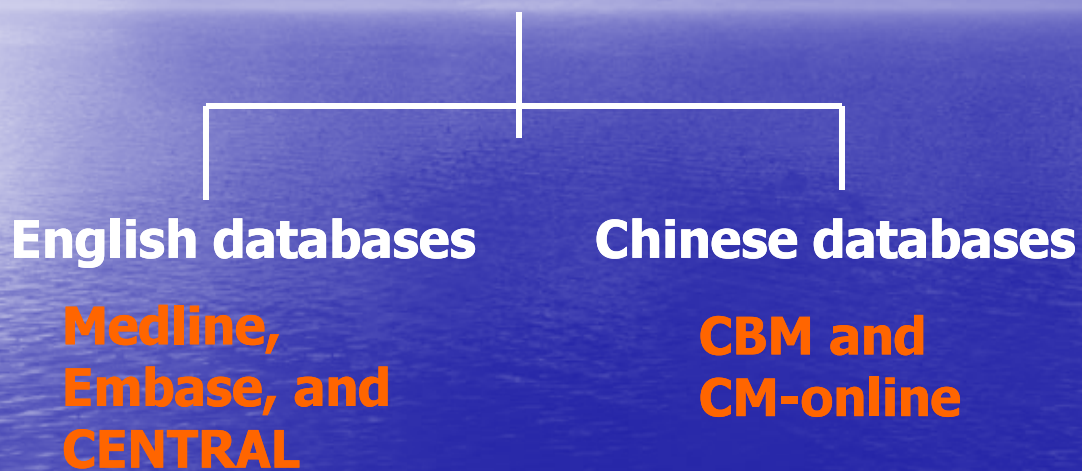
Search strategy:

- **Search strategy was developed around free-texts or subject headings about pain, cancer and Chinese herbal medicine.**

- **The search strategies for Medline and CBM were listed as follows:**

Medline

- 1 exp Pain/ or exp Neuralgia/ or exp Analgesics/
- 2 (pain or neuralgia or analgesic$).mp.
- 3 1 or 2
- 4 exp Neoplasms/
- 5 (cancer or tumuor).mp.
- 6 4 or 5
- 7 3 and 6
- 8 exp Medicine, Chinese Traditional/ or exp Drugs, Chinese Herbal/
- 9 chinese herbal medicine.mp. or chinese medicin$.mp.
- 10 8 or 9
- 11 7 and 10
- 12 limit 11 to humans

CBM and CM-online

- Search strategy in Chinese
- 1. (疼痛 or 痛證 or 鎮痛 or 止痛 or 麻醉) and (癌 or 腫瘤)
- 2. (癌痛)
- 3. 1 or 2
- 2. (中醫 or 中藥 or 植物藥 or 草藥)
- 3. 隨機 or 安慰 or 盲法 or 雙盲 or 單盲 or 三盲
- 4. 1 and 2 and 3
- 5. limit to human

Results – 1. Search results

Flow diagram showing the search process and study selection

Studies identified from databases and other sources (n=753)

Duplicate records excluded (n=69)

Articles screened for titles and abstracts (n=684)

Irrelevant records excluded (n=594)
Articles whose full texts were not available (n=2)

Full-text of RCTs retrieved for detailed evaluation (n=88)

Included studies for review (n=7)

Chinese herbal medicine vs. placebo (n=3)

Included for meta-analysis (n=3)

Chinese herbal medicine vs. analgesics (n=4)

Included for meta-analysis (n=2), 2 studies were excluded for meta-analysis due to the high risk of bias introduced by high dropout rates (>20%)

Results – 2. Effect results

(1) Chinese herbal medicine vs placebo

- Outcome 1: pain reduction (measured by the proportions of effectiveness or otherwise)
  - effective means pain is alleviated,
  - not effective means pain is not alleviated or even aggravated.

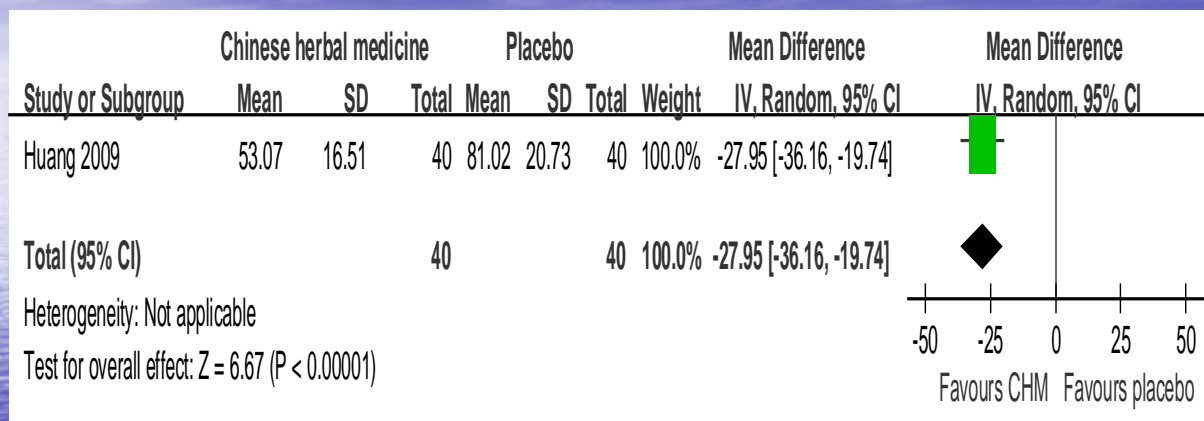| Study or Subgroup	Chinese herbal medicine Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
2.1.1 with supportive care							
He 2007	21	32	2	31	28.3%	27.68 [5.54, 138.20]	
Subtotal (95% CI)		32		31	28.3%	27.68 [5.54, 138.20]	
Total events	21		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 4.05 (P < 0.0001)							
2.1.2 without supportive care							
Liu 1988	164	177	91	155	71.7%	8.87 [4.64, 16.98]	
Subtotal (95% CI)		177		155	71.7%	8.87 [4.64, 16.98]	
Total events	164		91				
Heterogeneity: Not applicable							
Test for overall effect: Z = 6.59 (P < 0.00001)							
Total (95% CI)		209		186	100.0%	12.24 [4.48, 33.43]	
Total events	185		93				
Heterogeneity: Tau² = 0.26; Chi² = 1.66, df = 1 (P = 0.20); I² = 40%							
Test for overall effect: Z = 4.89 (P < 0.00001)							
Test for subgroup differences: Not applicable							

0.005   0.1   1   10   200
Favours placebo   Favours CHM

There is a significant difference between CHM and placebo in relieving cancer pain favoring CHM treatment.

Outcome 2: Analgesic (morphine) consumption

Study or Subgroup	Chinese herbal medicine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Huang 2009	53.07	16.51	40	81.02	20.73	40	100.0%	-27.95 [-36.16, -19.74]	
Total (95% CI)			40			40	100.0%	-27.95 [-36.16, -19.74]	

Heterogeneity: Not applicable
Test for overall effect: Z = 6.67 (P < 0.00001)

-50   -25   0   25   50
Favours CHM   Favours placebo

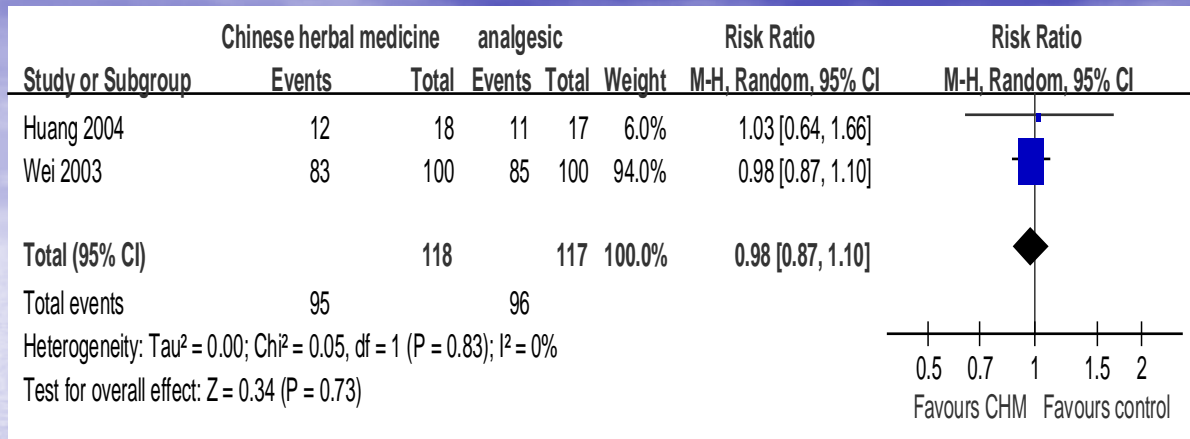**Chinese herbal medicine showed statistically significant effect on reducing the consumption of morphine when compared to placebo (mean difference 27.95mg, 95%CI 19.74 to 36.16).**

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(2) Chinese herbal medicine vs analgesics

- Outcome 1: pain reduction (measured by the proportions of effectiveness or otherwise)
  - effective means pain is alleviated,
  - not effective means pain is not alleviated or even aggravated.

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	Chinese herbal medicine		analgesic			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Huang 2004	12	18	11	17	6.0%	1.03 [0.64, 1.66]	
Wei 2003	83	100	85	100	94.0%	0.98 [0.87, 1.10]	
Total (95% CI)		118		117	100.0%	0.98 [0.87, 1.10]	
Total events	95		96				

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%

Test for overall effect: Z = 0.34 (P = 0.73)

0.5 0.7 1 1.5 2
Favours CHM Favours control

The analgesics used in the two studies were paracetamol/codeine phosphate (Wei 2003) and indomethacin (Huang 2004), respectively.

The proportion of patients whose pain was alleviated by CHM was similar to that by paracetamol/codeine phosphate (Wei 2003) or indomethacin (Huang 2004).

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Table 1. Treatment characteristics of the included studies on Chinese herbal medicine for cancer pain.

Study	Compositions	Administration route	Dosage	Treatment duration (day)
Liu 1988	蟾酥膏（蟾酥、生川烏、七葉一枝花, 紅花、莪朮、冰片等），製成橡皮膏	Paste on the pain area	Once per day	7
Huang 2009	癌理通膏（白藥膏、蟾酥、制馬錢子、毛麝香、寮刁竹、大梅片、金牛皮、冰片等）	Paste on the pain area	Twice per day	10
He 2007	康艾注射液（黃芪、人參、苦參）and 5% glucose solution 40ml or saline solution 250ml	Intravenous Infusion	Once per day	21
Wei 2003	天蟾膠囊（夏天無、制川烏、蟾酥、祖司麻、白芷、白芍、白屈菜、秦艽、川芎、甘草等）	Oral intake	3 capsules per time, 3 times per day	5
Huang 2004	溫陽止痛膠囊（熟地黃、鹿茸、肉桂、白芥子、甘草等）	Oral intake	4 capsules per time, 3 times per day	7
Chen 2000 & Lu 2001	桂參止痛合劑（由肉桂、細辛、黨參、杜仲等）	Oral intake	50ml per time, once every 8 hours	7

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Conclusions

- There is some evidence to show that Chinese herbal medicine may reduce the cancer pain intensity and exert similar pain relief effect similar to some analgesics.
- The conclusions drawn are off-set by methodological limitation such as no assessment of placebo blinding effect, high loss to follow-up and the low number of clinical trials.
- More information is also needed about the adverse effects of the treatment of Chinese herbal medicine.
- Further well-designed studies are needed to establish the efficacy and safety of Chinese herbal medicine for cancer pain.

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