

Review

Transdermal Pain Palliative Agents Containing Chinese Medicinal Herbs

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Abstract

The TCM (traditional Chinese medicine) transdermal plaster (also known as "cataplasma") are flexible adhesive patches used for treatment of any pain, resulted from arthritis, sprain and bruise, tendovaginitis, lumbar spine protrude, neuralgia, hyperosteoarthritis, abdominal discomfort and metastatic cancer, etc. This paper provides a review of the TCM transdermal agents for pain palliation and the preparation of these herbal patches.

Key words: Transdermal patch, traditional Chinese medicine, pain-palliative herbs

Introduction

Pain is believed as a symptom of some form of physiological disruption of function. Traditional medicine believed that the reason some people suffer more pain than others, often during a similar or identical illness, is due to the relative strength or balance of the innate temperaments of the body parts, and the strength of the force that opposes it (Long 1998). Most forms of pain including abdominal pain and cramps, headaches, lower back pain, and similar discomfort, are generally treated with a chemical drug symptomatically. That is, a drug is administered to shield the body's pain sensors and bring relief. The most frequently used chemicals for pain palliation belong to the group of so called "nonsteroidal anti-inflammatory drugs (NSAID)", such as aspirin. All NSAIDs share the following potential toxicities: hepatitis, renal dysfunction, sodium and fluid retention, gastrointestinal irritation (dyspepsia, nausea or vomiting, peptic

ulceration with or without hemorrhage or perforation), skin rash, and central nervous system symptoms (headaches, dizziness, blurred vision). The methodology of treating pain by traditional Chinese medicine differs from that of Western medicine, in that drugs are not used to shield or block the pain sensors, but to promote the local or systemic blood flow and remove blood stasis (Liang 1995). That is, the pain relief is achieved by dispersing the swelling and stasis responsible for pain and discomfort with extracts from certain medicinal herbs.

Many of the herbal extracts have been documented in traditional Chinese medicine (TCM) as having clinical effectiveness in removing blood stasis and alleviating local swelling and pain (Reid 1999). Other extracts and derivatives have been found effective in improving the microcirculation and immunity, and therefore, having the palliative effect on patients with painful bone lesion or diseases including rheumatoid arthritis and osteoarthritis. The medicinal herbs listed in the following are known to be prescribed in TCM for the treatment of pain of various kinds (Zhang et al. 2002).

Acacia catechu (Catechu)
Borneolum Syntheticum (Borneol)
Caulis Bambusae in Taenia (Cassia Twig)
Cortex Cercis chinensis (Chinese redbud)
Cortex Cinnamomi Cassiae (Cinnamon)
Cortex Phellodendri (Amur Cork-tree Bark)
Flos Carthami (Safflower)
Folium Hibisci Mutabilis (Coffonrose Hibiscus Leaf)
Fructus Toosendan (Szechwan Chinaberry Fruit)
Herba Asari Heterotropoidedis (Chinese Wild Ginger)
Herba Menthae Haplocalycis (Mint)
Lignum Aquilariae sinensis (Chinese Eaglewood Wood)
Ligusticum chuanxiong (Szechwan Lovage Rhizome)

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Moschus sifanicus (Musk)
Olibanum (Mastic Tree)
Pericarpium Papaveris (Opium Poppy Shell)
Radix Acomiti (Aconite Root)
Radix Aconiti Kusnezoffii (Kusnezoff Monkshood Root)
Radix Angelicae Dahuricae (Taiwan Angelica Root)
Radix Angelicae Pubescentis (Doubleteeth Pubescent Angelica Root)
Radix Angelicae sinensis (Chinese Angelica)
Radix Aucklandiae (Costus Root)
Radix Clematidis chinensis (Chinese Clematis Root)
Radix Dipsaci (Teasel)
Radix et Rhizoma Rhei (Rhubarb)
Radix Notoginseng (Gynura Pinnatifida)
Radix Paeoniae Alba (White Peony Root)
Radix Salviae Miltiorrhizae (Dan-Shen Root)
Radix Saposhnikoviae Divaricatae (Divaricate Saposhniovia Root)
Rhizoma Arisaematis (Jackinthepulpit Tuber)
Rhizoma Bletillae (Common Bletilla Tuber)
Rhizoma Corydalis (Corydalis Ambigua)
Rhizoma Curcumae Aeruginosae (Aeruginous Turmeric Rhizome)
Rhizoma et Radix Notopterygii (Angelica pubescens)
Rhizoma Kaempferiae (Kaempferia Root)
Rhizoma Polygoni Cuspidati (Giant Knotweed Rhizome)
Semen Alpiniae Katsumadai (Katsumade Galangal Seed)
Semen Strychni (Nux Vomica)

These medicinal herbs possess the actions of promoting blood flow to regulate menstruation, stasis breaking and lumps resolving, removing blood stasis and relieving pain, subduing swelling and promoting tissue regeneration, and so on. Therefore, they are applicable in relieving headache, thoracalgia, abdominal pain, dysmenorrhea due to blood stasis, and

traumatic ecchymoma, arthralgia-syndrome, septicema from carbuncle, and other symptoms. Although each of the above listed medicinal herbs has blood-activating and pain-relieving effectiveness, blend of extracts comprising several of the herbs or plants are used traditionally for better therapeutic efficacy (Jia 2002).

TCM Transdermal patches for pain relief

Historically, delivery of herbal drugs through the skin has been limited to a handful of agents containing simple herbal formula that readily traverse the skin's outermost layer known as the stratum corneum. The major reason for this limitation is the nature of herbs which contain multiple ingredients with different molecular sizes and chemical properties, which are not effective when used in small quantity and are slow in passing the inherent barrier of the skin. Conventional excipients including rubber and rosin were used as adhesives as well as drug carrier. These materials, although capable of holding the herbal extracts and facilitating the penetration of the extracts across the skin, often caused undesirable side effects such as skin irritation. Research in the field of traditional Chinese medicine has been motivated, to a large extent, by the desire to enhance the transdermal drug delivery system for treatment of local or systemic diseases. Since early 90's, investigators in China have used modern "patch" delivery systems for herbal drugs and obtained satisfactory results (Yan et al. 1992; Yi et al. 1998), especially from the treatment of various types of pain associated with bone diseases, abdominal discomfort, and tumors, etc.

Table 1 listed all the TCM transdermal patches that are under development or have been approved by Chinese health agency, known as State Drug Administration (SDA) (Jia et al. 2002).

Each transdermal agent listed in Table 1 consists of several

Table 1. TCM Transdermal patches for pain relief

Name	Company	Status
Zijing Healing Patch	Shanghai Leiyunshang Pharmaceuticals	approved in 1999
Bone-companion	Shi-yi-tang Topical Drugs, Herbin Pharma	available on the market
Yi-tie-ling Patch	Capital Pharmaceuticals of Chongqing	approved in 1999
Bone-recover Patch	Thousand-crops Pharmaceuticals of Xi-an	approved in 1996
Arthritic Bone Patch	The Henan TCM College	under development
Bone-soothing Patch	The Chengdu TCM University	under development
Bone-ease Patch	The Guangzhou TCM University	under development
Tumor-regression Patch	The Nanjing TCM Hospital	under development
Tumor-pain Patch	The Tianheng Pharmaceutical Research	pre-clinical
Pain-relief Patch	The College of Pharmaceutical Science & Technology, Tianjin University	pre-clinical

herbs in its formula (Yang et al. 2000; Mei 2000; Tang et al. 2001; Xu et al. 1996; Wang et al. 1998; Li et al. 1998; Li 1999; Jia et al. 2002). These formulas are summarized.

Preparation of TCM transdermal agents

Jia and Gao (2002) reviewed the compositions of TCM transdermal patches (also known as “cataplasma”), which typically consist of three layers of materials, backing layer, the drug matrix, and protecting layer.

The backing layer is a supporting material on which the drug matrix containing active TCM ingredients is applied or coated. The material of backing layer is typically made of woven fabrics of cotton, non-woven cloth, or flannel. The protecting layer which is selected from the following materials, polyethylene, cellophane, or aluminum foil, provides a cover for the TCM drug matrix. The middle part of the transdermal patch, between the backing layer and the protecting layer, is drug matrix, which consists of TCM extracts, adhesives, transdermal enhancers, water-preserve materials, filler, etc. All the excipients used in a

transdermal patch (see Figure 1) are selected from the following chemicals, depending on the drug ingredients, indication, and parts of the body the patch is to be applied.

Adhesives are selected from the these polymers: alginate sodium, Arabic gum, corn starch, gelatin, methyl cellulose (MC), polyacrylate sodium, polyvinyl alcohol (PVAL), polyvinyl pyrrolidone (PVP), sodium carboxymethyl cellulose (CMC-Na), sorbitol, tragacanth. Water-preserve materials include glycerin, polyethylene glycol, propylene glycol, sorbitol, etc. Filler materials include some inert or inorganic compounds such as bentonite, calcium carbonate, kaolin clay, silicone, titanium dioxide, zinc oxide. Transdermal enhancers are azone, dimethyl sulfoxide, eucalyptus oil, mint oil, synthetic borneol, etc.

A typical process for preparing the TCM patch is illustrated in Figure 2. The drug ingredients, i.e. the herbal extracts, are mixed with all excipients, and the drug matrix, also known as a drug reservoir system filled with herbal extracts and water-containing polymers, was formed. The drug matrix is then coated evenly on the surface of backing layer which is typically elastic non-woven cloth. After the polyethylene sheet or aluminum foil

Table 2. TCM patches and their formulas

Transdermal Agents	Ingredients
Zijing Healing Patch	Containing 22 herbs including <i>Cortex Cercis chinensis</i> , <i>Rhizoma et Radix Notopterygii</i> , <i>Radix Angelicae Pubescentis</i> , <i>Radix Angelicae Dahuricae</i> , <i>Ligusticum chuanxiong</i> , <i>Radix Angelicae sinensis</i> , <i>Radix Salviae Miltiorrhizae</i> , <i>Semen Strychni</i> , <i>Radix glycyrrhizae</i> , etc.
Bone-companion	Containing <i>Flos Carthami</i> , <i>Radix Dipsaci</i> , <i>Rhizoma Corydalis</i> , <i>Radix Saposhnikoviae</i> , <i>Periostracum Cicadae</i> , <i>Caulis Mucunae Sempervirentis</i> , <i>Radix Polygoni Multiflori</i> , <i>Radix Clematidis chinensis</i> , <i>Radix Acomiti</i> .
Yi-tie-ling Patch	Containing <i>Realgar</i> , <i>Oleum Eucalypti</i> , <i>Mentholum</i> , <i>Camphor</i> , <i>Borneolum Syntheticum</i> , etc.
Bone-recover Patch	Containing <i>Ramulus Taxilli</i> , <i>Lignum Aquilariae sinensis</i> , <i>Cortex Phellodendri</i> , <i>Herba Cayratiae japonicae</i> , <i>Copper</i> , etc.
Arthritic Bone Patch	Containing <i>Olibanu</i> , <i>Commiphora myrrha</i> , <i>Acacia catechu</i> , <i>Resina Ferulae</i> , <i>Flos Caryophylli</i> , <i>Cortex Cinnamomi Cassiae</i> , <i>Camphor</i> , <i>Moschus sifanicus</i> , etc.
Bone-soothing Patch	Containing 10 herbs including <i>Cortex Phellodendri</i> , <i>Rhizoma Curcumae Longae</i> , <i>Radix Angelicae Dahuricae</i> , <i>Radix et Rhizoma Rhei</i> , etc.
Bone-ease Patch	Containing <i>Radix et Rhizoma Rhei</i> , <i>Cortex Phellodendri</i> , <i>Cacumen Platycladi</i> , <i>Borneolum Syntheticum</i> , <i>Mentholum</i> , etc.
Tumor-regression Patch	Containing <i>Radix Acomiti</i> , <i>Radix Salviae Miltiorrhizae</i> , <i>Radix Sophorae tonkinensis</i> , <i>Rhizoma Curcumae</i> , etc.
Tumor-pain Patch	Containing <i>Rhizoma Corydalis</i> , <i>Aconitum camichaeli</i> , etc.
Pain-relief Patch	Containing <i>Rhizoma Corydalis</i> , <i>Fructus Toosendan</i> .

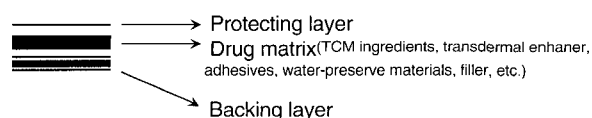


Figure 1. Typical structure of TCM transdermal patch

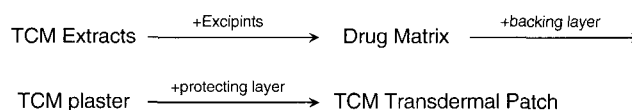


Figure 2. Typical process of TCM patch preparation

is pressurized on the top of the drug matrix, the TCM patch is completed and ready for cutting and packaging. The TCM drug matrix typically consists of 5-15% of herbal extracts, 40-60% of water, 10-15% of inorganic materials as filler, 1-5% of transdermal enhancing materials, 5-15% of adhesives, and 5-15% of other excipients (Zhang et al. 2001; Jia 2000; Fan 1995; Yang 1991; Zheng 1997).

Treatment of pain using TCM agents

Topically applicable herbal preparations are preferred formulations with respect to the treatment comfort of the patient. In contrast to oral or parenteral formulations, a topical formulation can be applied to the place of treatment easily and painlessly even by the patient. Another advantage of topical formulations is that the patient can, either at first sight or by touching his skin, easily ascertain whether he has applied the medicine or not, thereby the risk of inadvertent overdosing or underdosing considerably decreases.

The TCM transdermal patches are used for the treatment of pain of various kinds including bone pain, muscle pain and abdominal pain. Bone pain may result from trauma, overuse, infection, primary bone cancer, metastatic cancer, loss of mineralization (osteoporosis), disruption of blood supply (as in sickle cell anemia), and other less common conditions. Muscle pain is a common complaint. It is most frequently related to overuse or muscle injury due to exercise or physically demanding work. In these situations, the muscle pain tends to involve rather specific muscles or muscle groups, and the cause of the muscle pain is fairly obvious. Abdominal pain may result from diseases including hepatitis, ulcers in G.I. tract, cholecystitis, cholelith, etc. There are no effective chemical drugs that will relieve the pressing pain associated with gallstone and cholecystitis.

Generally, blend of extracts comprising several of the medicinal herbs are used clinically for better results of pain relief or palliation. Different herbal compositions in TCM formulas are organized by certain rules following the TCM theory of treating a specific disease (Jia et al. 2002). A typical rule, known as the Four Responsible Roles, is often used to select herbs based on the role each herb plays in the drug formula. The Four Roles are called King, Minister, Assistant, and Servant. The King is the principal active herb in the formula, selected for its known therapeutic benefits for specific ailments. The Minister's role is to assist and reinforce the principal active herb, while the Assistant is usually added to neutralize any side effects of the King and Minister herbs. The role of the servant is to harmonize the actions of all the other ingredients and to enhance their absorption into the bloodstream, organs, or target tissues.

The use of a TCM patch system (also known as "cataplas-

ma") is advantageous in that the lipophilic and hydrophilic ingredients of the herbal extracts are solubilized and then "gellified" with the organic polymers, and that the drug matrix containing up to 70% of water serves as a "drug reservoir" that will sustain the quick and continuous release of herbal ingredients over several days across the skin.

The principle of palliative treatment for painful bone metastasis is the combined use of the most effective and convenient techniques that have the least side-effects. While there are conventional remedies for palliation of pain and discomfort associated with cancer or other bone diseases, administration of oral drugs and supplements combined with transdermal palliative herbal agents may significantly alleviate the symptoms and improve their quality of life.

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