

Traditional Chinese medicine in dermatology

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ABSTRACT: Traditional Chinese medicine (TCM) is an alternative method of therapy that can be administered in oral, topical, or injectable forms. It emphasizes the importance of using many herbs that are combined in different formulations for each individual patient. Since it is not possible to discuss all applications of TCM in every skin disorder, psoriasis and atopic dermatitis are used as the prototypes in illustrating the use of TCM. A number of studies have shown the usefulness of TCM in the treatment of these skin conditions, and thus it is worthwhile for dermatologists throughout the West to gain some familiarity with this method. We attempt to provide a general overview of TCM through a discussion of efficacy, mechanisms of action, and side effects of various TCMs. A warning regarding the possible contamination of TCMs is also included. In the future, perhaps a better understanding of TCM will be gained through more systematic analysis and controlled studies with a placebo arm. It is our hope that this article will provide dermatologists with a more complete understanding of the role and ramifications of TCM therapy.

KEYWORDS: atopic dermatitis, complementary, Oriental, psoriasis, traditional Chinese medicine.

Traditional Chinese medicine (TCM) is an alternative therapy that can be used in the treatment of dermatologic disorders, including various forms of psoriasis. In general, TCM stresses the importance of catering the therapy to the needs of each individual, as opposed to Western therapeutic approaches that are standardized and stress “average” efficacy in large, double-blind, placebo-controlled studies. This fundamental difference has led many clinicians to practice primarily Western medicine, which is viewed as “more scientific,” leaving no room for TCM in either the inpatient or outpatient setting. Of interest is that patients appear to be more receptive to alternative medicine. A recent study found that 51% of a population of psoriasis patients opted to use such alternative therapies as herbal remedies, vitamin supplements, and dietary manipulation (this figure excludes the use of sunlight and nonprescription tanning equipment) (1). Another study found that in a population of patients with psoriasis,

those interested in getting alternative treatment (69%) were willing to spend an average of \$450 for alternative treatment. Dissatisfaction with their conventional treatment was the most common reason cited for their interest in alternative therapy (2). Because complimentary therapies, including TCM, are widely used, it is imperative for practicing clinicians to understand these agents. Even practitioners who have no intention of using TCM in their own clinics should be trained to identify side effects and contraindications that occur with these drugs.

Due to a lack of familiarity with this field, a number of misconceptions about TCM may be held by dermatologists. The most prevalent misconception seems to be that there are no reliable double-blind, placebo-controlled studies on TCM other than the ones conducted in England—one in children (3) and one in adults (4)—for atopic dermatitis. The truth is that there have been a number of controlled and comparison studies of TCM conducted in mainland China and other East Asian countries, including Japan. There is also the notion that the mechanism of action of traditional Chinese medications has not been

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investigated or worked out. In fact, there are many published scientific papers from China and Western nations that elucidate the mechanism of action for a number of TCM therapies. The last and perhaps the most clinically relevant misconception is that TCM has no side effects because it uses “natural” substances. This view, held by some clinicians and many patients, can lead to unnecessary complications and even fatalities if appropriate measures are not taken quickly enough. Many experienced practitioners of TCM are well aware of the possible side effects that can occur with various TCM drugs and drug combinations, and exercise great caution in their use.

These topics could be expanded on to take up volumes of books, however, in the interest of brevity the authors hope to provide a general appreciation and overview of this field in the space provided.

Efficacy

A growing awareness among Western dermatologists of the effectiveness of TCM as being more than simply a placebo came about as a result of a double-blind, placebo-controlled trial of TCM for atopic dermatitis carried out at the Hospital for Sick Children, London, England. In this clinical trial, a Chinese physician, Dr. Luo, formulated a mixture of 10 herbs for the treatment of atopic dermatitis: *Clematis armandii*, *Dictamnus dasycarpus*, *Glycyrrhiza glabrae*, *Ledebouriella saseloides*, *Lophatherum gracile*, *Rehmannia glutinosa*, *Paeonia lactiflora*, *Potentilla chinensis*, *Tribulus terrestris*, and *Schizonepeta tenuifolia*. These herbs were ground, placed in porous paper sachets, and boiled. The patients then drank the decoction. The placebo sachets had a similar taste, smell, and appearance, however, they did not contain the “right” constellation of herbs for treatment of atopic dermatitis. In this double-blind, placebo-controlled crossover study, there was a clear distinction between the genuine TCM therapy and the placebo herbs. With the active herbs there was a median decrease in erythema of 91.4% and a decrease in the extent of surface involvement of 85.7%. This can be compared to the placebo group, which had decreases of 10.6% and 17.3%, respectively. There were no abnormalities seen in the liver function tests, renal function tests, and complete blood counts.

A 1-year follow-up of both children and adults who chose to continue to use TCM showed a persistent benefit with only minimal side effects.

This is in contrast to the clinical deterioration of patients who elected to discontinue use of TCM in the ensuing year (5,6). Of interest is that many of the patients, both children and adults, who chose to continue TCM were able to decrease the frequency of their TCM to less than daily use, while still others were able to discontinue treatment altogether without experiencing a relapse. Two of the children that elected to use TCM in the follow-up year had an asymptomatic elevation of serum aspartate aminotransferase, which normalized 8 weeks after discontinuing the medication. There were no biochemical abnormalities seen among the adults using TCM in the follow-up year.

The aforementioned study is the best-known efficacy study in the literature to date on TCM. Most of these types of studies are published in Chinese medical journals that rarely get translated into English or any other language. Therefore the authors would like to recognize Dr. Xi-Ran Lin, the Chairman of the Department of Dermatology, Dailen Medical Center, People's Republic of China, for offering his help in obtaining information from Chinese publications. The findings in various journals, both Western and Chinese, are summarized below with a focus on psoriasis as a prototype for chronic skin disease. The authors will explore TCM therapies that include the use of oral, topical, photochemotherapeutic, and injectable agents. In addition, the authors will discuss the efficacy of therapeutic groups of agents and explore the use of acupuncture in psoriasis.

In an open study involving 86 psoriasis patients, indirubin, an active ingredient found in *Indigo naturalis*, was used in dosages ranging from 100 to 300 mg/day, and compared with patients treated with ethyliminum 300 mg/day. Although ethyliminum is no longer used in Western medicine for psoriasis treatment, it is still considered to be a Western remedy in China. The study concluded that indirubin was the more efficacious drug of the two (7). Side effects of indirubin were primarily gastrointestinal and were reported in 26–96% of patients, varying by series, with some rating the side effects as “severe” (7–11).

To decrease the side effects, indirubin was molecularly modified, resulting in the formation of N-methylisoidindotin (meisoindigo) and N-acetylindirubin (12–14). Subsequently a dose-range study demonstrated that meisoindigo had better efficacy at 150 mg/day rather than 75 mg/day. Commercially, a prepared composite of *I. naturalis*—pillulae *Indigo naturalis compositae*—is already

available and widely marketed in China. This premade capsule has fewer side effects than *I. naturalis* alone (15). In an open study, oral pillulae Indigo naturalis was as efficacious as ethyliminum with fewer side effects (16). As of 1993, the results obtained from treating 636 research subjects showed that three patients had a transient abnormality in their liver function tests, while three others had transient decreases in their peripheral white blood cell counts (7–16).

The Chinese medical literature describes another oral agent, *Tripterygium wilfordii* Hook, which was used in 638 cases of plaque-type psoriasis, along with 37 cases of psoriatic arthritis, 16 cases of pustular psoriasis, and 5 cases of erythrodermic psoriasis with good therapeutic benefit (17–23). Investigation into its mechanism of action has shown that it has both anti-inflammatory and immunosuppressive activity. Side effects both in animals and humans include gastrointestinal reactions, abnormal menstruation, and cutaneous/mucocutaneous reactions. Furthermore, there have been reports of abnormal liver function and exacerbation of latent hepatitis (17). It has been unclear as to whether or not there are adverse effects involving the hematopoietic system. A related compound, *Tripterygium hypoglaucum* Hutch, has been shown in open studies to have similar efficacy, but without significant side effects (24–26).

Another medicine, *Camptotheca acuminata* Decne, was found to be too toxic as a systemic medication and was relegated to topical use instead. It comes from a plant found in southern China and has been shown to be very efficacious (27). This herb contains numerous alkaloids that have antineoplastic activity, including camptothecin, 10-, 11-, or 12-hydroxycamptothecin, 9-, 10-, or 11-methoxycamptothecin, 12-chlorocamptothecin, venoterpin, and deoxycamptothecin (28,29). In an open trial with 92 psoriasis patients, topical treatment of 0.03% *C. acuminata* Decne was found to be more effective than 1% hydrocortisone. Comparison with such a weak topical steroid is unfortunate, because at best the hydrocortisone treatment may be regarded as a placebo. Side effects included contact dermatitis in 9–15% of the subjects and a possible enhancement of postinflammatory hyperpigmentation.

Another herb, *Radix angelicae dahuricae*, contains furocoumarins such as imperatorin, isoimperatorin, and alloimperatorin, which combine with DNA just like psoralen plus ultraviolet A (PUVA) (30). A multicenter study involving 13 hospitals compared the therapeutic efficacy of the

oral use of *R. angelicae dahuricae* in association with UVA irradiation with traditional PUVA phototherapy conducted with 8-MOP (31). Of the 204 patients treated with *R. angelicae dahuricae*-UVA therapy, 133 (46.8%) were cleared and 121 (42.6%) were almost cleared of their psoriasis. In comparison, in 92 patients that were treated with PUVA phototherapy, 40 (43.5%) were cleared and 43 (46.7%) were almost cleared. Although there was no statistical advantage to either treatment, most subjects preferred the use of the *R. angelicae dahuricae*-UVA therapy because of its relatively milder side effects. The side effects of *R. angelicae dahuricae*-UVA therapy appear to be similar to those of 8-MOP and include dizziness and nausea.

A second phototherapeutic herb, *Radix angelicae pubescentis*, was also used in conjunction with UVA irradiation. In a study involving 92 patients, 62 cleared their psoriasis with relatively mild side effects (32). Noteworthy is that changes in the lens were reported with long-term use of *R. angelicae pubescentis*-UVA therapy (33).

A common herb, green tea, has also been studied to understand its role as a possible adjuvant in photochemotherapeutic psoriasis treatment. It has been found that green tea extracts are beneficial in preventing early signs of photochemical damage to human skin treated with PUVA therapy. PUVA, a treatment for psoriasis, increases the risk of developing squamous cell carcinoma and possibly melanoma (controversial) in Caucasian patients. Pretreatment and posttreatment with green tea extracts significantly decreased markers of this photochemical damage, namely hyperplasia and hyperkeratosis, c-fos/p53, and erythema ($p < 0.05$), when compared with controls (water given before and after treatment) (34).

In addition to the oral, topical, and photochemotherapeutic agents that have already been described, there are some forms of injectable TCM. In an open study, 50 patients with psoriasis were treated with an injectable form of *Radix macrotomiae seu lithospermi*. Of those treated, 13 were cleared and 26 had significant improvement without any systemic side effects (35).

The aforementioned drugs have all been relatively easy to discuss and study for efficacy because they are used as monotherapies in treating psoriasis. They are often preformulated with precise dosages and known compositions. However, this constitutes only one part of TCM. As mentioned earlier, TCM focuses on using many herbs that are combined in different ways for different patients. Often this means blending more

than 10 different herbs and other therapeutic agents into a single formulation. These formulations are subtly modified based on the specific clinical presentation and characteristics unique to the individual. The specific combination utilized is often changed over time, according to the clinical status of the patient.

In TCM, diagnostic criteria used to assess patients are often very different from those used in Western medicine. There may be a mystique surrounding the complicated and incomprehensible ingredients used in various illnesses, however, most TCM preparations can be grouped into three major classes according to their use: aches/pains, orthopedic injury, and skin diseases. There are many other areas of medical practice where TCM is not as widely used due to the perception that it is less efficacious in those areas. In each class, the ingredients revolve around a common theme, with only minor differences made on a case-by-case basis (36). We will focus once again on the category of skin diseases, using psoriasis as a model.

According to TCM, psoriasis is subtyped into several categories, such as “blood-heat,” “blood deficiency-dryness,” and “blood stasis.” Different formulations are made depending on the subtype of psoriasis that is diagnosed. For example, the “blood stasis” type is characterized by a psoriatic lesion that is very indurated and has little tendency to resolve. Associated diagnostic features include a dark red or purplish-colored tongue with some petechia and a pulse that is described as “small and loose.” Treatment of the “blood stasis” type of psoriasis is aimed at “activating the blood and eliminating the stasis.” Common herbs used as core ingredients in treatment include *Rhizoma sparganii*, *Rhizoma curoumae*, *Semen persicae*, *Flos carthami*, *Caulis spatholob*, *Ramulus euonymi*, *Herba hedyotis diffusae*, and *Pericarpium citri reticulatae*. To this core list, TCM practitioners would typically add or substitute other herbs that would be appropriate to the individual being treated.

The herbal remedies are often prepared by boiling and are taken as oral solutions. Not surprisingly, the “blood deficiency-dryness” type of psoriasis is marked by different physical findings and requires a different set of herbs for therapy. This type of psoriasis is noteworthy because patients have tongues that have a “pinkish color with a thin coating.” Measurements for tongue color and pulse quality are not usually used in Western hospitals, so it is difficult to corroborate these clinical finding among American patients.

Due to the overwhelming variability in how patients are treated, both between TCM practitioners and within the practice of a single TCM practitioner, it is challenging to carry out a controlled therapeutic trial to study the traditional approach of individual polypharmacy. However, some open studies have been done to compare the efficacy of traditional approaches and Western therapeutic agents. In one study, 206 cases of psoriasis were treated with TCM and 52 cases were treated with oral bimecizumab 600 mg/day. Both were found to be efficacious, with no significant difference favoring either approach. At the time, the only difference was that there were three cases of leukopenia within the bimecizumab-treated group, whereas there were no biochemical or hematologic abnormalities in the TCM-treated group. In addition, in a 3-year follow-up study, it was found that the TCM-treated group had a significantly lower recurrence rate than the bimecizumab-treated group (37).

Another open study followed the use of a mixture of five herbs—*Rhizoma sparganii*, *Rhizoma zedoariae*, *Herba serissae*, *Resina boswelliae*, and *Myrrha*—in 801 psoriatic patients. The investigators found a 50–85% response rate among these patients. In addition, a 6-year follow-up study compared the efficacy of yet another group of herbs. The herbs were used to treat 41 cases of psoriasis, while 106 cases of psoriasis were treated with etanercept. The study found that etanercept had greater short-term efficacy, however, the remission time was significantly longer with the use of TCM ($p < 0.01$) (38).

Unfortunately the data on effective psoriasis treatment are not quite so supportive of other Chinese medicines such as acupuncture. The author (J. Koo) has been to mainland China many times, and the overall impression of the author in interacting with clinical and academic dermatology leaders in the People's Republic of China is that acupuncture is generally not efficacious for dermatologic diseases. In the worldwide literature, there is only one controlled trial of acupuncture in psoriasis patients. The study involved 56 patients, half of whom received the active therapy provided by a licensed acupuncturist, consisting of proper placement of needles with sufficient depth followed by proper electrical stimulation. The other 28 patients received placebo treatment, which meant that needles were purposely placed 1 cm outside the recommended location, placement was deliberately made too superficial for optimal benefit, and electrical stimulation was not given. After twice-weekly treatments for 10

weeks, there was no clear benefit of the acupuncture treatment over the placebo treatment. In fact, the placebo group did better on overall psoriasis area and severity index (PASI) scores, which are a reflection of the severity of skin lesions (39). Outside of this study, all of the other published reports have made sweeping claims either without substantial evidence (40,41) or without proper controls (42), or have been described in journals that are difficult to obtain (43,44).

Mechanism of action

Of all of the studies mentioned, the one that received the most recognition was the one that showed the efficacy of TCM in atopic dermatitis. In response, many studies have been conducted to better understand the mechanism of action behind Dr. Luo's 10-herb combination. The primary focus is currently on the impact that the herbs have on expression of CD23, an IgE receptor that is implicated in the pathogenesis of atopic dermatitis. The receptor exists in two forms: type A is constitutively expressed in B cells, and type B is induced by interleukin (IL)-4 in a variety of cells (45–47). CD23 is excessively expressed in monocytes and in the skin of individuals affected by atopic dermatitis (48–50). This may be the consequence of having lymphocytes that are known to produce higher levels of IL-4 (51,52), another finding in atopic dermatitis. Studies have shown that the combination of 10 herbs used in the Sheehan et al. (4) investigation were found to have a strong, dose-dependent, inhibitory effect on CD23 expression in peripheral blood monocytes, an effect that was not observed in the placebo group. The inhibition does not seem to be a result of monocyte death because peripheral mononuclear cells cultured with TCM, at the same concentrations used in the study, had the same viability as control cultures. This finding was supported by a second study conducted by Xu et al. (53) of the Royal Free Hospital and School of Medicine in London. In addition, Dr. Xu's group noticed a significant reduction in human leukocyte antigen (HLA)-DR expression in cells treated with the TCM herbs. Lastly, a third group in England was able to show that the TCM herbal medications, when compared to the placebo drugs, had significant antioxidant effects. The study involved using a 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assay, which detects the donation of a hydrogen atom from an antioxidant to an enzyme (DPPH) that contains a stable free radical, and a superoxide scavenging assay.

In addition to the now-famous 10-herb formulation of Dr. Luo, other Chinese medicines have been analyzed for their mechanism of action. For example, a Chinese traditional medicine marketed in Japan as an antihistamine/antiallergy medication called *Sho-seiryu-to* has been extensively studied. The herb seems to inhibit histamine release from rat mast cells and inhibit the increase in vascular permeability induced by histamine (54). It also profoundly inhibits 48-hour passive cutaneous anaphylactic reactions in rats. *Sho-seiryu-to* was found to have no effect on histamine H₁ receptors and the muscarinic/cholinergic system in the brain, accounting for the lack of sedative side effects. Another Japanese study looked at a traditional Chinese medicine called *Moku-boi-to*. Once again, in rats, it was found that *Moku-boi-to* significantly reduced the skin reaction induced by antigen-antibody complexes and suppressed the capillary permeability induced by histamine, LTC₄, and antiserum. The antihistamine effect was actually equipotent to the optimal dose of Western antihistamines such as diphenhydramine (55).

Side effects

Unfortunately many patients subscribe to the belief that herbal medications are without adverse effects because they are "natural." Physicians often do not question patients about their use of herbal supplements, and patients are reluctant to divulge the use of these agents for fear of criticism from their physician. It is important for physicians to become aware of the most common and the most serious side effects of herbs to aid in better patient education, as well as better diagnosis of very rare but possibly fatal sequelae (56).

Many cutaneous reactions to herbal preparations have been reported, the most common being allergic contact dermatitis. Two patients developed erythroderma after using topical herbal treatments for psoriasis and atopic dermatitis, and one developed Stevens-Johnson syndrome after taking "Golden Health blood purifying tablets," which contained multiple herbs, including red clover, burdock, queen's delight, poke root, prickly ash, sassafras bark, and *Passiflora* (57). In fact, an article discussing contact dermatitis from TCM reports that "side effects of Chinese medicinal material are not rare" (58). Dr. Li further states that "hypersensitivity, hepatic toxicity and renal damage have all been reported in China, some of which have been fatal" (59,60). He

then goes on to describe cases where contact dermatitis has developed in response to Chinese herbal medications.

In agreement with Dr. Li's statements are documented cases of adverse systemic effects including hepatotoxicity, cardiotoxicity, and respiratory distress, some of which have been fatal on occasion. There is a case of a 29-year-old British woman who died from acute liver failure following the use of TCM (61). She had two prior episodes of hepatitis following the use of a Chinese herbal treatment for eczema. After her second hospitalization she developed acute liver failure and died in spite of an emergency liver transplant. As a result of cases like this, the Working Group on Dietary Supplements and Health Foods in the United Kingdom recommended the establishment of a reporting scheme for adverse reactions from these products (62). From January 1991 to December 1993, a total of 11 cases of liver damage following the use of Chinese herbal medicines for skin conditions were reported to this agency.

It is strongly suspected that the etiology of these cases was the herb, although it cannot be established unequivocally. This is especially true in cases where the recovery occurred after discontinuation of the herbal medicine and then recurred after the patient was rechallenged with the same herb. The immediate cause-effect time course and the lack of another causative agent further establish the herb as the likely etiologic factor. In seven of these cases, the herbal material was available for analysis; however, the plant mixtures varied from case to case, yielding no single ingredient as the culprit. In these 11 cases, liver damage did not seem to be dose dependent and was probably idiosyncratic. Based on these findings, the authors recommend regular liver function test monitoring for patients who take oral TCMs (63).

There is also a case of reversible dilated cardiomyopathy that developed in a 42-year-old woman after treatment of atopic dermatitis with a 2-week course of TCM (64). The herbal preparation contained more than 30 herbal components and it was therefore impossible to identify the causative agent. Another report from Japan describes a 59-year-old woman who developed adult respiratory distress syndrome following the use of Chinese herbal medications for seborrheic dermatitis (65). The authors recommend that Chinese herbal medicines be held to the same drug licensing, monitoring, and surveillance procedures as any new drug entering the United Kingdom.

An important consideration when evaluating the side effects of herbs is the quality control

that goes into the final product. It may not be the main therapeutic agent or its vehicle that is at fault, rather it may be that the medication is contaminated with the presence of an underlying prescription drug or some other toxic agent. A report from St. Paul, Minnesota, described patients who used Chinese herbal preparations that were contaminated with various undeclared prescription drugs ranging from nonsteroidal anti-inflammatory drugs (NSAIDs) to diazepam. The article describes a patient who developed massive gastrointestinal bleeding after ingesting a Chinese herbal medication that was found to contain a high dose of prescription NSAIDs. Various authors have revealed that Chinese herbal medications may contain betamethasone, chlordiazepoxide, dexamethasone, diazepam, hydrocortisone, indomethacin, nefenamic acid, methyltestosterone, prednisolone, prednisone, or lead and other heavy metals. Additional substances reported in the literature as contaminants of herbal medicines include aminopyrine, caffeine, chlorpheniramine, chlorzoxazone, ethaverine, hydrochlorothiazide, paracetamol, phenylbutazone, and thiamine.

Chinese herbal medicines are not tightly regulated by government agencies, unlike their prescription medication counterparts. There are no quality-control measures currently in place in the United States to ensure the purity, concentration, or safety of herbal supplements. Although herb manufacturers are restricted from making efficacy statements, there are no regulations on claims about which symptoms these herbs can alleviate. In the United States, there are also no regulations on which herbs can be restricted in formulations (66). Due to this poor quality control, there is a real danger of undeclared prescription medications masquerading as herbal medicines and also of accidental contamination that may result in toxicity.

Conclusion

It is a shame that many dermatologists practicing in the United States have little understanding of the use of TCM in skin conditions. The topic is of paramount importance since many patients use these agents either in conjunction with or in place of "orthodox" Western medications. There is mounting evidence that supports the very real possibility that TCM is efficacious, but it is also important to remember the risk of adverse effects that can accompany the use of these agents. Even though clinical studies are regularly conducted

and reported in the Chinese medical literature, the use of a placebo arm is still relatively rare. To complicate matters, the Western medications used for comparison in mainland China are frequently not the agents that are currently being used in the Western world, making interpretation of the results difficult. Lastly, the totally different approach of TCM, emphasizing the use of individualized polypharmacy, may make sense to clinicians in possibly hitting many facets of the inflammatory process simultaneously, especially for chronic inflammatory skin diseases such as eczema and psoriasis. This may be why there seems to be a consensus among Western-trained doctors working in mainland China that despite a relative paucity of rigorous clinical trial data, herbal TCM is useful and safe in treating patients with certain types of chronic or intractable illness. Perhaps even more telling is that this opinion seems more strongly held among those physicians that had practiced TCM for a longer period of time (67). Unfortunately the use of this approach makes scientific analysis extremely difficult.

As this analysis unfolds in the coming years it will be important for Western clinicians to get a handle on the large volume of data on herbal therapies and other alternative therapies. This may be accomplished with the use of some excellent Internet resources and catalogs that maintain up-to-date information on a wide range of alternative therapies (68). With an aware and receptive audience, the stage is set for a more systematic, rigorous analysis and testing of therapeutic agents used in TCM that may eventually lead to the development of useful therapeutic agents for the entire world.

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