ARTICLE

Traditional Chinese Medicine for the Treatment of Dermatologic Disorders

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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. Among some segments of the patient population, it has become increasingly popular as a mode for treating dermatologic diseases. As a result, it is now worthwhile for dermatologists throughout the West to gain some familiarity with this method. Yet, dermatologists are largely unfamiliar with TCM and may possess some misconceptions. We attempt to give a general overview of TCM through the discussion of different clinical studies involving various TCMs. Some proposed mechanisms of action of TCM are also presented. A discussion of adverse effects, including hepatotoxic effects and the need for close monitoring is discussed. A warning regarding the possible contamination of TCMs is also included. Since it is not possible to discuss the application of TCM for every skin disorder, psoriasis and atopic dermatitis are used as the prototype in illustrating the use of TCM. 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 an overview of the efficacy, mechanism of action, as well as adverse effects of TCM.

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Herbal medicine uses any plant part such as the root, bark, stem, seed, flowers, or leaves as a means for treatment. Many of the modern drugs now used are based on "native herbal wisdom." For example, medications like anthralin, aspirin, and alkaloids were originally herbal medications.

There are 3 basic functions that herbal medicines purportedly perform: elimination and detoxification, health management and maintenance, and health building.[1]

Herbal medical practitioners can create many different formulas for different types of applications. The formulation is contingent on the circumstances, condition being treated, type or part of the plant used, and the characteristics of the individual treated.

Most dermatologists in the United States have expertise in administering "orthodox" therapies. These dermatologists are basically knowledgeable of those therapies that are sanctioned by the Food and Drug Administration. There is usually support for these therapies in scientific medical literature, particularly literature published in the English language. However, many patients who are frustrated with orthodox medicine often decide to explore alternative therapies.

Fleischer and colleagues[2] found in a recent survey that 5% of a patient population with psoriasis have used alternative therapies, excluding the use of sunlight and nonprescription tanning equipment. Among these are dietary manipulation, herbal remedies, and vitamin therapy.

Alternative therapies have become more widely used because of increasing interest among patients. Traditional Chinese medicine (TCM) is of particular significance because it is a common choice of patients. Thus, it has become relevant for practicing dermatologists to be reasonably knowledgeable about this field. Whether administering TCM or not, it is intrinsically

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imperative to have an accurate perspective. In this manner, one can be properly aware of possible adverse effects from use of TCM by the patient. Many practicing dermatologists in the United States possess certain misconceptions regarding TCM because of their lack of familiarity with this field.

To begin with, some dermatologists may be still unaware of the existence of placebo-controlled studies involving TCM. There are 2 double-blind, placebo-controlled studies on TCM that have been published in the English-language medical literature. One has been conducted with children[3] and the other with adults.[4] These studies were carried out in England using TCM to treat atopic dermatitis. Many studies have also been published in Asian countries such as Japan and mainland China.

Another misconception is that detailed scientific investigation of the mechanism of action of TCM has never been conducted. Yet, several countries including China have published scientific articles on the proposed mechanism of action of TCM and further studies are being carried out.

One truly unfortunate misconception is that TCM has no adverse effects due to its natural composition. This is a misleading notion in that many people, possibly including some physicians automatically assume that natural compounds are benign. However, experienced practitioners are aware that oral TCMs have possible adverse effects such as hepatotoxicity. A common concern with topical TCM is contact dermatitis.

Our goal is to provide a general overview and understanding of this field, since a comprehensive coverage of TCM is not possible herein. A complete description of TCM would be exhaustive because of the numerous agents involved to treat almost every possible dermatologic condition.

EFFICIENCY OF TCM

Sheehan and colleagues[3] working with Luo, a Chinese herbalist in London, England, performed one of the first double-blind, placebo-controlled studies with TCM in the West. The positive findings were a surprise for many Western dermatologists. The study consisted of a double-blind, placebo-controlled trial using TCM to treat atopic dermatitis. It was performed at the Hospital for Sick Children in London.

Luo incorporated 10 herbs in the therapeutic agent.[3,5] These herbs were *Potentilla chinensis, Tribulus terrestris, Rehmannia glutinosa, Lophatherum gracile, Clematis armandii, Ledebouriella saseloides, Dictamnus dasycarpus, Paeonia lactiflora, Schizonepeta tenuifolia,* and *Glycyrrhiza glabrae*. The herbs were first ground, then placed in porous paper sachets, and boiled down into a thick concentrate and strained. This decoction was then orally administered to each patient in the form of a drink. The placebo consisted of a different assortment of herbs that had no known efficacy for the treatment of atopic dermatitis. However, the sachets were similar in taste, smell, and appearance.

At the end of the treatment period, the median decrease in erythema was 91.4% with the active herbs and 10.6% with the placebo herbs. The active herbs also contributed to an 85.7% decrease in the extent of surface involvement scores, while there was a 17.3% decrease with the placebo herbs.

During the study period there were no apparent abnormalities in liver function tests, renal function tests, and complete blood cell counts. A follow-up study (of both children and adults) was conducted a year later. Those who elected to continue with TCM maintained the benefits of the therapy with minimal adverse effects. In contrast, those who discontinued the treatment experienced a decline in their condition.[6,7] Over time many of the patients, both pediatric and adult, were able to minimize their usage of TCM and most of them eventually discontinued the treatment without a relapse. The adult patients, who continued the treatment for 1 year, did not exhibit any biochemical abnormalities. However, 2 of the pediatric subjects developed asymptomatic elevation of serum aspartate aminotransferase levels. Yet, once the medication was discontinued the elevated level normalized within 8 weeks.

Many efficacy studies have been performed, but the study by Luo is the best known in the English-language literature.[3,5] Most other studies are only published in Chinese medical journals. Many of them have never been translated into another language. Yet, the Chinese publications contain a plethora of valuable information essential for understanding TCM.

Although TCM has been used to treat a variety of skin diseases, of particular interest to us is psoriasis. Both topical and systemic use of herbs has been administered to treat psoriasis, as well as a combination of herbal medications with UV-A. This method is similar to psoralen–UV-A phototherapy.

Radix Angelicae pubescentis is a Chinese herbal medicine that is administered in combination with UV-A irradiation. A study[8] was conducted in 92 cases, 62 of these patients were successfully cleared of psoriasis. However, they exhibited relatively mild adverse effects. With long-term use it was found that there were changes in the lens.[9]

Furocoumarins, including imperatorin, isoimpertorin, and alloimperatorin are found in another Chinese herbal medicine, *Radix Angelicae dahuricae*. Psoralen compounds are formed from the combination of *Radix Angelicae dahuricae* with UV-A irradiation and DNA.[10] A study[11] involving 13 hospitals was conducted to assess the therapeutic efficacy of the oral use of *Radix Angelicae dahuricae* in combination with UV-A irradiation. The results were compared with traditional psoralen–UV-A phototherapy conducted with 8-methoxypsoralen.[11] *Radix Angelicae dahuricae* UV-A therapy was used to treat 204 patients with psoriasis. The treatment was successful in clearing psoriasis in 133 patients (46.8%) and inducing marked improvement in 121 patients (42.6%) in whom psoriasis was not completely cleared. Psoralen–UV-A phototherapy was administered in 92 patients with psoriasis. Forty patients (43.5%) were cleared whereas 43 (46.7%) exhibited marked improvement. The difference in the efficacy of treatments between psoralen–UV-A phototherapy and *Radix Angelicae dahuricae* UV-A therapy was not statistically significant. The only perceived difference was the severity of adverse effects. *Radix Angelicae dahuricae* exhibited milder adverse effects than 8-MOP. The adverse effects included nausea and dizziness.

Tripterygium wilfordii Hook and *Triptergium hypoglaucum Hutch* are 2 popular TCMs. *Tripterygium wilfordii Hook* has yielded positive therapeutic effects when used to treat various types of psoriasis. The Chinese medical literature has recorded 638 cases of plaque-type psoriasis, 37 cases of psoriatic arthritis, 16 cases of pustular

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psoriasis, and 5 cases of erythrodermic psoriasis that have been treated with *Tripterygium wilfordii Hook*.[12-18] Although *Tripterygium wilfordii Hook's* possible mechanism of action has been investigated to be both anti-inflammatory and immunosuppressive, there have been several negative consequences.

Some toxic effects have been observed in both animals and human subjects. Among these are gastrointestinal reaction, cutaneous/mucotaneous reactions, and abnormal menstruation. Some abnormalities in the hematopoietic system were also noted. In addition, exacerbation of latent chronic hepatitis and abnormal liver function was observed in several cases.

The clinical efficacy is similar for *Triptergium hypoglaucum Hutch* and *Tripterygium wilfordii Hook*. Chinese medical literature concludes that with the current results *Tripterygium wilfordii Hook* and *Triptergium hypoglaucum Hutch* have shown modest efficacy with an acceptable adverse effects profile.[19-21]

Another Chinese herbal medication has been analyzed in a study involving 86 patients with psoriasis with indirubin, an active ingredient found in *Indigo natualis*. Indirubin was administered in dosages varying from 100 to 300 mg/d. This was compared with ethyliminum treatment of 300 mg/d. Ethyliminum is popular in China as a "Western remedy" although it is no longer incorporated in Western medicine for psoriasis.

As a result of this study, indirubin was discovered to be more effective than ethyliminum.[22] The adverse effects of indirubin and *I natualis* were found to be mainly gastrointestinal. There was a wide range in reported adverse effects from as low as 26% to as high as 96% with some being rated as "severe."[22-26] Molecular modification of indirubin was conducted to decrease the adverse effects. Two new compounds *N*-methylisoindigotin (meisoindigo) and *N*-acetyl-indirubin were developed.[27-29]

Indigo natualis is also incorporated in *Pillulae Indigo natualis compositae,* a commercially prepared composite medicine widely marketed in China. This capsule was found to be beneficial in that it had fewer adverse effects than *I natualis* used by itself.[30]

The efficacy of oral *P Indigo natualis compositae* was evaluated in an open study. Its efficacy for psoriasis was equivalent to that of oral ethyliminum with a positive difference—fewer adverse effects.[31] As of 1993, 636 research subjects have been treated with *I nautalis* or other diindole compounds.[22-31] Among the findings published in Chinese medical literature, there is a record of 6 cases of adverse effects consisting of 3 instances of transient cases of abnormality in liver function tests, and another 3 occurrences of transient decreases in peripheral white blood cell counts.

Some TCMs that have demonstrated systemic efficacy are formulated as topical agents. This is particularly true of those medications found to be too toxic with systemic use. A plant from the southern provinces of China, *Camptotheca acuminata decne*, is one example.[32] Alkaloids with antineoplastic activities including camptotheca, 10-, 11-, or 12-hydroxycamptotheic, deoxycamptotheic, 12-chlorocamptotheic, 9-, 10-, or 11-methoxycamptothecin, and venoterpin are found in this herb.[33,34]

The efficacy of *Camptotheca acuminata decne* was studied in an open trial involving 92 cases of psoriasis. A 0.03% concentration of topical *Camptotheca acuminata decne* was compared with a 1% hydrocortisone. *Camptotheca acuminata decne* was determined to be significantly more effective. A possible weakness of this study is the choice of 1% hydrocortisone, a weak topical steroid, as a comparison. It is perhaps more appropriately considered a placebo arm of the study. Contact dermatitis was found in 9% to 15% of the subjects studied and the researchers also noticed possible enhancement of postinflammatory hyperpigmentation.

Although TCMs are commonly found in topical, oral, and photochemotherapeutic modalities, some of them are also injectable. Sometimes the injectable agent yields better results than when used in the other forms. For instance, *Radix macrotomiae seu Lithospermi* when injected resulted in a more significant therapeutic effect in treating psoriasis than in an oral formulation. An open study of 50 patients led to 13 cleared of psoriasis and 26 greatly improved without systemic adverse effects.[35]

The TCMs discussed so far are similar to Western medications in that they are marketed as capsules or tablets that are taken orally. These are the more modern, convenient, and more user-friendly prepackaged TCM preparations. They are formulated as monotherapies or in groups of herbs. However, these agents compose only a small fraction of TCM practice.

The standard TCM practice emphasizes the importance of using many herbs combined in different compositions for each individual patient. The formulation is based on the diagnosis and individual condition of the patient. Whereas Western medicine emphasizes monotherapy, standard TCM promotes herbal mixtures sometimes involving more than 10 different herbs and other agents.

According to TCM, psoriasis is subtyped into 3 main categories: "blood-heat" type, "blood deficiency-dryness" type, and "blood stasis" type. According to the subtype of psoriasis the patient has, a different mixture of herbs is suggested.

For example, when inflicted with blood stasis psoriasis the lesions are indurated and have little tendency to resolve spontaneously. There is also a purplish or dark red coloring of the tongue with occasional petechia. The pulse is often small and loose.

The principle of treatment of this type of psoriasis is to activate the blood and eliminate the stasis. The most often used prescriptions include *Herba Hedyotis diffusae, Flos carthami, Semen persicae, Ramulus euonymi, Rhizoma sparganii, Rhizoma curoumae, Pericarpium Citri reticulatae*, and *Caulis spatholob*. These are only the core ingredients that are recommended. They are ingested as decoctions. According to the needs of each patient, this list would be altered.

To treat blood deficiency-dryness a different set of herbs is considered more suitable. Among the physical manifestations of this type is the appearance of the tongue characterized by pinkish color with a thin coating. Western dermatologists do not routinely inspect the tongues or pulses of their patients with psoriasis. Thus, it is difficult to make a comparison between patients in China and those in the United States.

Since the judgment of the practitioner determines the unique herbal mixture for each individual patient, it is difficult to conduct a controlled trial. The more traditional

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practice of TCM involves enormous variation. Yet, a few open studies have been conducted in China comparing Western therapeutic agents with traditional approaches.

One open study[3] evaluated 206 patients with psoriasis treated with traditional approaches. They were compared with 52 patients with psoriasis treated with 600 mg/d of oral bimolanum. Both groups were found to be fairly equivalent in efficiency. Among the 52 patients treated with bimolanum there were 3 cases of leukopenia. There were no hematological or biochemical abnormalities among the 206 patients treated with TCM. Another advantage of TCM was that in a follow-up study[36] 3 years later it was found that patients treated with TCM had a significantly lower recurrence rate than those treated with oral bimolanum.

In another open study,[37] 801 patients with psoriasis were treated with a different mixture of herbs. These were *Herba serissae, Myrrha, Rhizoma zedoariae, Resina boswelliae,* and *Rhizoma sparganii*. There was an interesting 50% to 85% response rate among the 801 patients.

Another investigation involved a 6-year follow-up study of 41 patients with psoriasis treated with TCM and 106 patients treated with ethyliminum. A different mixture of herbs was administered in this study. The short-term efficacy of ethyliminum was better than that of this particular combination of Chinese medical herbs. However, the remission time was longer with TCM. Statistically there was a significant difference between the 2 groups in favor of TCM ($P<.01$).[37]

No discussion of TCM would be complete without considering acupuncture. It is highly doubtful as to whether acupuncture has any efficacy in a skin disorder such as psoriasis. For the last 5 years, one of us (J.K.) has traveled to mainland China every year. After interacting with prominent academic and clinical dermatology pioneers in China, the general consensus was that acupuncture is not considered efficacious for treatment of skin disease.

The medical literature has an account of only 1 controlled trial[38] of acupuncture for psoriasis. Of 56 patients, 28 received active therapy by proper placement of needles followed by electrical stimulation. The other 28 patients consisted of the placebo group. The needles were placed 1 cm away from the proper location at an insufficient depth. In addition, no electrical stimulation was applied. The treatments were administered twice weekly for 10 weeks. At the conclusion of this trial, there was no significant difference between the 2 groups. The investigators of this study[38] were led to conclude that classic acupuncture was not any more efficacious than placebo. Amazingly, the placebo group did better overall on the psoriasis area severity index evaluation. Other published reports do not have proper controls,[39] make claims without verifiable evidence,[40,41] or have been described in obscure journals.[42,43] Thus, acupuncture as a viable alternative therapy in dermatology has not been substantiated.

MECHANISM OF ACTION OF TCM

The 10-herb combination of Luo as a treatment of atopic dermatitis has become widely known among Western dermatologists.[5] Consequently, several studies have been conducted to extrapolate the mechanism of action of these herbs. Currently, the focus of the investigation has been on the impact of the herbal mixture on CD23 expression.

CD23, an IgE receptor, has been implicated in the pathogenesis of atopic dermatitis. CD23 is present in 2 forms: type A, which is solely expressed on B cells, and type B, which can be induced by interleukin 4 to be expressed on a variety of cells.[44-46] In patients with atopic dermatitis, excessive expression of IgE receptor 23 has been found in monocytes.[47,48] In addition, they also have an increased expression of CD23 in their skin.[49] A possible explanation of this may be that the lymphocytes of patients with atopic dermatitis are known to produce a higher level of interleukin 4.[50,51] Some authors[5] conducted studies with the combination of the 10 herbs of Luo. They found that the herbal combination had a strong inhibitory effect on CD23 expression on peripheral blood monocytes. The placebo combination was found to have no effect on CD23 expression.

The inhibition of CD23 expression was discovered to be dose dependent. Furthermore, the mechanism of the inhibition was not due to the death of monocytes. Those peripheral mononuclear cells cultured with TCM or placebo at the same concentration as the original experiments had a similar viability to control cultures.

Xu and colleagues[52] of the Royal Free Hospital and School of Medicine in London confirmed the above findings in their publication. In addition, Xu et al found a significant reduction in HLA-DR expression. Another study from England demonstrated that the formulation of the 10 Chinese herbs when administered in vitro exhibited significant anti-oxidant activity.

Although the 10-herb formulation by Luo is well known,[3] other TCMs have also been analyzed to understand their mechanism of action. Several of these studies have been performed in countries outside of China such as Japan.

Matsumoto and colleagues[53] have been compiling data on Shor-seiryu-to, which is a TCM that is marketed in Japan as an antihistamine/antiallergy medication. Matsumoto et al found that the effectiveness of Shor-seiryu-to is due to the inhibition of histamine release based on the data from studies on rat mast cells. Another study conducted by Sakaguchi et al[54] discovered Shor-seiryu-to to have a profound effect in inhibiting 48-hour passive cutaneous anaphylactic reaction in rats. It also significantly inhibited an increase in vascular permeability induced by histamine. Shor-seiryu-to had no sedative adverse effects. This was due to Shor-seiryu-to not affecting $histamine_1$ receptors and the muscarinic cholinergic system in the brain.

Moku-boi-to is another TCM that is marketed in Japan. Data compiled through Japanese studies performed on this medicine found moku-boi-to to profoundly suppress the enhancement of capillary permeability induced by histamine, LTC_4 (leukotriene C_4), and antiserum in the rat skin. When compared with the optimal dosage of a Western anthihistamine such as diphenhydramine, moku-boi-to was equipotent in antihistaminic effect.[55] In conclusion, moku-boi-to was found to have suppressive effects on chemical mediators of inflammation such as histamine and LTC_4. In addition, it also reduces the effect of the antigen-antibody response in the skin.

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ADVERSE EFFECTS

It is a common misconception that natural medications, such as herbal medicine, is a safer mode of therapy because of its presumed lack of adverse effects. However, it is well documented that herbal medications used in TCM can have serious adverse systemic effects such as hepatotoxicity. Li,[56] a physician from the People's Republic of China reports that "side effects of Chinese medicinal material are not rare." In addition, "hypersensitivity, hepatic toxicity and renal damage have all been reported in China, some of which have been fatal."[57,58] There was even a report[59] from Japan of a 59-year-old woman who developed adult respiratory distress syndrome after use of TCM for seborrheic dermatitis.

Liver complications, including elevated liver function test results and acute liver failure are one of the most well-documented adverse effects of TCM. In Great Britain,[60] a 29-year-old woman was prescribed Chinese herbal treatment for eczema. She consequently developed 2 episodes of hepatitis that led to hospitalization. She had acute liver failure after the second hospitalization. This later led to her death, despite an emergency liver transplantation.[60] In response to such incidents, The Working Group on Dietary Supplements and Health Foods in the United Kingdom has taken steps to establish a reporting scheme for adverse reactions related to the use of TCM.[61]

The British governmental agency has recorded 11 cases of liver damage following the use of TCM for skin conditions from January 1991 to December 1993. In many of the cases, recovery occurred after discontinuation of the herbal medicines. Later when rechallenged with the same herbal medicine, there was a recurrence of hepatitis. Although it is difficult to establish absolute etiologic association for all 11 cases, there is an obvious circumstantial link between TCM and the consequent liver damage.

In these reported cases, there is a good chronological relationship with the absence of a viable alternative explanation for the liver damage. The herbal material was analyzed for 7 of the above 11 cases. Yet, due to the variance in the plant mixtures for each individual, no single ingredient could be extrapolated as the sole cause of the liver injury. Furthermore, the analysis of the 11 cases revealed that the liver damage was not dose related, but was most likely idiosyncratic. The authors[62] highly recommend regular liver function testing as a means for monitoring patients prescribed oral TCM.

To illustrate another case of an adverse effect of TCM,[63] consider a 42-year-old woman who developed severe cardiomyopathy following a course of TCM. She had been prescribed TCM for 2 weeks to treat her eczema. An herbal analysis, conducted later, revealed that the formulation contained more than 30 herbs. Once again, it was not possible to decisively conclude any one ingredient as the cause for the congestive cardiomyopathy.

In the hopes of determining any future adverse effects, we recommend that Chinese herbal medications be subjected to drug licensing, monitoring, and surveillance procedures. This should be done in a manner similar to what any new drug is subjected to for approval in the United States or United Kingdom.

Currently, there is an unfortunate possibility that because of the lack of quality control an herbal medication may be contaminated with undeclared prescription drugs. This may lead to adverse reactions in the patients. In St Paul, Minn, a report[62] was published that detailed the case of several patients who had been given contaminated Chinese herbal preparations. Various undeclared prescription drugs, ranging from nonsteroidal anti-inflammatory drugs to diazepam were discovered in these formulations. One particular patient developed massive gastrointestinal bleeding after ingesting a Chinese herbal medication that was later found to contain a high dose of prescription nonsteroidal anti-inflammatory medication.

Various authors have previously published analyses of Chinese herbal medications. These findings have revealed many types of contaminants. Methyltestosterone, dexamethasone, indomethacin, chlordiazepoxide, prednisolone, betamethasone, lead, diazepam, nefenamic acid, prednisone, or hydrocortisone are are some of many substances that have been found in these medications. Other possible contaminants of Chinese herbal medications include hydrochlorothiazide, chlorpheniramine, pheynlbutazone, aminopyrine, paracetamol, thiamin, caffeine, and ethaverine. Regulation of Chinese herbal medications by governmental agencies is essential in maintaining quality control. Otherwise, there is a potential danger of undeclared prescription medications infiltrating Chinese herbal preparations and being unknowingly administered to patients.

CONCLUSIONS

Many practicing dermatologists in the United States are only familiar with orthodox Western procedures for the treatment of skin disorders. However, an increasing number of patients have begun to seek TCM as an alternative mode of therapy. It has been demonstrated in published studies that there is a real possibility that TCM has a substantial efficacy beyond a simple placebo effect. However, TCM has also been associated with notable adverse effects, some fatal. The current clinical studies in the Chinese medical literature are not a complete source of information about TCM. Many of the studies have been conducted without a placebo arm and it is difficult to interpret the results in comparison studies. This is so because the standard Western medications used for comparison in China are often not those agents currently used in Western medicine.

The individualized polypharmacy approach of TCM is intuitively sensible. This is especially in countering a complex, chronic, and often recalcitrant inflammatory process such as psoriasis or eczema in which it would be most beneficial to attack the process through many facets simultaneously. However, this approach would lead to extremely difficult scientific analysis of these medications. A more rigorous, systematic analysis and testing of therapeutic agents used in TCM may eventually lead to the development of a standard set of therapeutic agents that may be administered with reliable efficacy and good quality control.

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