

Practices, challenges, and opportunities: HIV/AIDS treatment with traditional Chinese medicine in China

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Abstract Traditional Chinese medicine (TCM) has become widely used in the treatment of acquired immune deficiency syndrome (AIDS) in China in recent years. In this article, we summarize the recent major developments in human immunodeficiency virus/AIDS (HIV/AIDS) treatment with TCM. The use of TCM is associated with preventing or alleviating HIV-related symptoms, reducing treatment side effects, and improving the quality of life. The potential beneficial effects of TCM should be confirmed through extensive and rigorous trials.

Keywords HIV/AIDS; traditional Chinese medicine

Introduction

Since the early 1980s, over 40 million individuals have been infected with HIV worldwide and over 12 million have died. In China, 370 393 cases of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) have been identified, as of October 2010, according to the Chinese Ministry of Health. The medical, social, and economic implications of HIV infection are devastating.

In 1996, the use of protease inhibitor therapy became widely available for treatment of HIV infection and resulted in a decline in HIV-related morbidity and mortality. Despite the effectiveness of the current antiretroviral therapies in suppressing disease progression, many HIV/AIDS patients report using traditional Chinese medicine (TCM) to manage HIV symptoms and side effects of conventional HIV medication and to improve their quality of life (QOL). Over the last decade, the use of TCM in mainland China has increased gradually among the population of HIV/AIDS patients. In this article, we review the recent major developments and future challenges in HIV/AIDS treatment with TCM in China.

TCM and AIDS

AIDS is a “new” disease, having only been identified in 1981, and thus, there is no specific research on the disease from the past or in classic literature. TCM possesses a large body of information about infectious diseases and epidemics and ways to describe the symptoms of patients with AIDS. AIDS can be defined in different ways according to TCM pattern identification. TCM uses the term “yi bing” (infectious epidemic diseases) to describe epidemic diseases such as AIDS, which are caused by invading evils (viruses). AIDS can also be considered a “pestilence,” which is “wen yi” in Chinese. Such a disease is regarded to have long latency, sudden onset, and severe symptoms. Diseases having similarity with HIV include “Xulao” (consumptive disease) and “Fuqi Wenbing” (incubative pathogen caused by epidemic febrile disease).

According to the adage, “western medicine treats the disease, whereas Chinese medicine treats the patient.” When an individual who has sufficient vital force and strong adjustment ability contracts HIV infection, he/she could live concurrently with infection and become a long-time HIV carrier, with retarded progression from the asymptomatic stage to the AIDS stage. TCM stresses the activity and adaptation of the organism to the pathogen. TCM therapy involves comprehensively treating patients using various measures, including Chinese drugs, acupuncture, moxibustion, and exercise, to enhance the immune function of the organism and to block the development, retard the initiation

(progression from the asymptomatic stage to the AIDS stage), or alleviate the signs and symptoms of the disease to improve QOL and prolong the life span of patients. The TCM used in intervention in treatment of HIV/AIDS depends on the stage of infection. For the asymptomatic stage (HIV carrier) patients, the key aim of TCM is to stimulate the body's defense mechanism to fend off diseases, which means "treatment before getting sick," and to maintain and enhance the immune function to delay the progression to the AIDS stage. For patients at the AIDS stage, TCM treatment focuses on relieving the symptoms of patients with AIDS-related opportunistic infection to improve their QOL or to combine with highly active antiretroviral therapy (HAART) to alleviate the side effects of biomedical drugs.

Chinese herbal medicine screening

Tens of thousands of herbs have been screened for anti-HIV activity. Some of them demonstrate ability to inhibit HIV, such as *Radix Arnebiae*, *Herba Viola*, *Flos Lonicerae*, *Flos Chrysanthemi Indici*, *Fructus Mume*, *Cortex Cinnamomi*, and *Fructus Ligustri Lucidi* [1–3]. In addition, bioactive materials extracted or isolated from medicinal herbs have been shown to inhibit HIV activity as well. These include polysaccharides (e.g. polysaccharides of *Radix Ginseng*, *Glossogyne tenuifolia* Cass, *Radix Astragali*, *Ganoderma Lucidum seu Japonicum*, and *Radix Actinidiae*), protein components (e.g. glucoprotein in aloe, a component from *Radix Trichosanthis*, alpha and beta momordicines in *Momordica charantia*, ricin bond A, and cimigenol saponin), alkaloids (e.g. castanospermine and colchicines), lactones (e.g. baicalein and hypericin), and terpenes (e.g. glycyrrhizin and goddypol).

Numerous herbs or herb extracts may attenuate the course of HIV infection through immune enhancement, cytokine stimulation, or other pathways. For example, *Radix Astragali* and *Cordyceps* have been reported to enhance T helper lymphocytes and to promote an optimal CD4/CD8 ratio [4,5]. In addition, shikonin has been shown to decrease the expression of CCR5 and CCR5 mRNA [6].

Despite their long history of use, many clinically proven Chinese herbal formulas lack a well-defined mechanism of action. Therefore, it is necessary to identify the active ingredient(s) of a herbal extract for an in-depth mechanistic investigation.

Clinical developments

Antiretroviral therapy can reduce morbidity and mortality, prolong lives, and improve the QOL of people living with HIV. However, HAART has some limitations, such as drug toxicities and cross-resistance among antiretroviral drugs of the same class. Accessing antiretroviral drugs is not convenient for patients in rural areas, and thus alternative approaches are required. TCM, which has been practiced for

centuries for health in China, is currently gaining popularity in the West. In the past decade, evidence from experimental studies and clinical trials has demonstrated a positive association between use of TCM and immune promotion and symptom relief of people living with HIV/AIDS. Numerous observational studies and randomized controlled trials (RCT) that compared herbal medicines or moxibustion with placebo or antiretroviral drugs in patients with HIV infection, HIV-related disease, or AIDS have shown that Chinese herbs as well as acupuncture and moxibustion reduce the signs and symptoms of AIDS and opportunistic infections, and improve immune function and QOL. Significant improvement has been reported in AIDS patients with diarrhea and some gastrointestinal dysfunctions. Specifically, 3 double blind RCT trials have reported that the use of regular Chinese herbs (i.e. Compound SH, Tangcao tablets, and Qiankunng capsules) for 6 months to 1 year significantly reduces the level of HIV transcripts compared with the placebo group [7–9]. Moreover, 2 double blind RCT trials have reported that the use of regular Chinese herbs (i.e. Aining Granule and ZY-4) for 6–11 months is associated with stabilizing and promoting the immune function compared with the placebo group [10,11]. The beneficial effects of Chinese herbs on immune function enhancement and symptom alleviation (e.g. fatigue, cough, diarrhea, and poor appetite) especially on those at the asymptomatic stage has been established in 49 observational studies [12]. Although a bias may be inherent in these observational data, these studies exhibit a wide variety of Chinese treatment principles, such as supplementing *Qi* and nourishing *Yin*, promoting *Qi* and activating blood circulation, clearing heat and dispelling dampness, and removing toxic substances.

AIDS-related disease

Chinese herbs have been used to treat AIDS-related diseases. Twelve RCT trials [13] have reported that Chinese herb use has a positive effect on oral candidiasis, peripheral neuropathy, skin rash, and diarrhea. For instance, Xiaomi Granules may contribute to the treatment of HIV-related oral candidiasis, whereas Shenlingbaizhu Decoction and Yiaikang capsule may treat HIV-related diarrhea. However, these findings still need to be confirmed through extensive and rigorous trials.

TCM and western medicine combination therapy

China's current national guidelines, updated in 2008, recommend ART initiation in all patients with a CD4 cell count of < 350 cells/mm³. This earlier initiation suggests that the use of Chinese herbs combined with HAART should be emphasized more. The use of Chinese herb medicines is associated with no or only slight adverse effects. However, the potential interaction between herbs and antiretroviral agents still needs to be explored, although it has been reported

that Aining Granule may prolong the metabolic duration of the anti-HIV drug Indinavir *in vivo*. Chinese herbal medicines may have some effect on chemical drugs by interacting with CYP450 in the liver [14]. Further pharmacokinetic studies to unveil the interactions between herbs and antiretroviral agents are urgently required, and the clinical significance of these interactions should be assessed.

Counteracting the side effects of HAART

The Chinese herb Aizhi 1 prescription has been reported to be effective in correcting the abnormal fat distribution caused by HAART, improve lipid condition, and increase CD4 cell count [15]. The Duhuoji sheng Decoction may improve peripheral neuropathy caused by HAART [16], Fuzheng-tongbi Decoction may alleviate peripheral neuritis [17], and the Chinese herb Kangaibaosheng capsule may contribute to the restoration of immune function of AIDS patients, enhance the efficacy of HAART, and improve QOL [18]. The Chinese herb Jingyuankang capsule may contribute to marrow suppression post-HAART [19]. A promising gastrointestinal benefit (i.e. bloated abdomen) has been found in Banxia-iexin Decoction [20].

TCM non-drug therapy

Three RCT trials have reported that warming moxibustion with the main points Shenque (CV8), Guanyuan (CV4), Zusanli (ST36), Zhongwan (CV12), and Tianshu (ST 25) has a positive effect on AIDS patients with diarrhea [21–23].

Evidence from these trials suggests that there are some beneficial effects of using herbal medicines and moxibustion for HIV infection and AIDS. However, considering the small sample and limitations of the trials (most trials had less than 30 participants and duration ranging from 3 months to a year), more evidence from extensive, well designed, and rigorous trials is required to support the findings. Therefore, future trials should be rigorous in methodology and address clinical outcomes such as patients' reported outcome, QOL, or symptom relief. Participants should be stratified according to their stages, such as asymptomatic HIV-infection, HIV-related diseases, or AIDS. The quality of herbal medicine to be tested should be guaranteed through *in vitro* or *in vivo* experimental studies, and adherence should be evaluated in the trials. A preliminary assessment system established to evaluate the effect of TCM in treating HIV/AIDS includes the following aspects: subjective symptoms of patients, QOL, signs and symptoms physicians are concerned about, clinical endpoints, and biological parameters, which are an excellent reflection of TCM efficacy [24].

According to the SFDA regulations in China, new Chinese medicine patents for the treatment of AIDS should be classified into anti-HIV patents verified through *in vitro* and *in vivo* experiments, and supplementary patents for AIDS treatments that either add synergistic effects or alleviate the

toxic side effects of existing antiretroviral drugs. Tangcao tablets are the first patent approved by SFDA for alleviating signs and symptoms of HIV/AIDS in patients; 5 other relatively mature compounds (i.e. Qiankunling tablets, Keaite capsule, Chuankezhi injection, Zhongyan-2 granules, and Compound Sanhuangsan) are still in clinical trials.

TCM intervention on HIV-positive individual and AIDS patients began in 2004. A pilot project called National Free TCM HIV/AIDS Treatment Program was launched by the State Administrative Bureau of Traditional Chinese Medicine and quickly scaled up from 5 provinces (i.e. Henan, Hebei, Anhui, Hubei, and Guangdong) to 19 provinces, autonomous regions, and municipalities in China, including places with high prevalence. Cumulatively, 9267 cases have been treated with TCM to date. The therapeutic effects in 8946 cases included in pilot projects are as follows: most of the cases maintained stable immune function; main signs and symptoms such as fever, cough, fatigue, poor appetite, and diarrhea significantly improved ($P < 0.001$); and no adverse reaction was found in TCM treatment. The results of the 3-year CD4⁺ lymphocyte count of 807 cases of HIV/AIDS enrolled in the program showed that the overall CD4⁺ lymphocyte count was maintained stably at the 6th and 12th months, declined significantly at the 18th, 24th, and 30th months, and then elevated to the pre-treatment level at the 36th month. Patients with a pre-treatment CD4⁺ lymphocyte count level $< 200/\text{mm}^3$, who combined HAART, had significantly elevated CD4⁺ lymphocyte counts after each visit. Patients with a pre-treatment CD4⁺ lymphocyte count between $200/\text{mm}^3$ and $350/\text{mm}^3$ maintained a stable CD4⁺ lymphocyte count before the 36th month, which then increased significantly, implying a long-term effect of TCM. Patients with a pre-treatment CD4⁺ lymphocyte count level $> 350/\text{mm}^3$ had a significant decrease in CD4⁺ lymphocyte count after all visits [25].

Challenges and opportunities

TCM, with its long history of use and detailed documentation in both theory and practice, has abundant experience in treating viral infectious diseases. Western medicine treats the disease, whereas TCM targets the patients with the disease. China is a developing country with many HIV/AIDS patients located in places with limited medical facilities and resources. TCM has advantages such as low price, rich resources, and accessibility. In contrast, HAART has the following limitations: drug resistance; side effects; reservoir of virus that cannot be removed; some patients demonstrate low viral load status and low CD4 level or are dissatisfied with QOL post-HAART; and unavailability of drugs for patients at the asymptomatic stage. These disadvantages present a great opportunity for TCM treatment. However, whether Chinese herbs have side effects, whether it produce synergistic or subdued effects with western medicine remains a challenge.

Specifically, finding the action mechanism of some Chinese herbs or recipes is difficult. In clinical research, there is a lack of extensive, well-designed, and rigorous trials, as well as the same TCM syndrome diagnostic criteria and a special TCM efficacy evaluation system. In addition, how to design a more proper clinical research plan and randomized controlled trial flow and how to evaluate the efficacy still remain an important problem.

Nevertheless, we firmly believe that TCM, with its long history of use and detailed documentation in both theory and practice, will play an important role in combating AIDS in the future.

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