

GUEST COMMENTARY

Clinical Immunology and Traditional Herbal Medicines

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The use of herbs to treat illness has its roots in an ancient holistic healing tradition that originated in Asia more than 3,000 years ago (10). Largely discounted by 19th and 20th century practitioners of Western medicine, healing practices incorporating herbal remedies, such as traditional Chinese medicine (TCM), Japanese Kampo, and Indian Ayurveda, are rapidly gaining acceptance in the West as we enter the 21st century. Herbal medicines are complex mixtures of minimally processed medicinal plants (e.g., plant parts that are boiled to make a tea). In conjunction with other components of traditional healing philosophies, such as acupuncture or massage, herbal medicines are used to treat a large range of symptoms and ailments, including liver disease, asthma, and other immune problems, menstrual problems, colds, headaches, and various cancers.

Explanations for the renaissance of traditional medical practices are numerous (4), but the reality is that herbal medicines and other natural or alternative treatment modalities are quickly being assimilated into Western medical practice. In the latter part of the 19th century, Japan adopted Western medicine as the official medical practice (1, 7), and today, many Japanese physicians are Western trained. Yet, in 1998, 75% of Japanese physicians who responded to a survey reported prescribing Kampo medicines, and the Japanese National Health Insurance plan currently covers Kampo treatment (1). Although 20th century China similarly adopted Western medicine as the orthodox treatment, a \$64 million Institute of Chinese Medicine currently is being built in Hong Kong, and Taiwan and mainland China also are pumping funds into the study of traditional formulas (11). Estimates are that in 1997 and 1998, Americans spent upwards of \$4 billion on herbal medicines (4).

American interest in traditional herbal remedies is not due solely to health food devotees or West Coast denizens. In January of this year, *Science* (11) reported the start of the first U.S. clinical trial of an anticancer drug derived from a traditional Chinese herbal remedy. Shanghai pharmacist Li Dapeng has isolated what seems to be the active component of the herb coix, which is used in many TCM preparations and the consumption of which epidemiologic studies show to be associated with low cancer rates. The mechanism of action is unknown, but Kangleite, the drug developed from coix, is the most popular anticancer medicine in China. The U.S. Food and Drug

Administration just approved a phase II trial to determine its efficacy in treating non-small-cell carcinoma.

Clinical and laboratory immunologists should find much interest in the increasing use of herbal medicines. Many herbal preparations alter immune function and have had an amazing array of immunomodulatory effects attributed to them (see the review of Kampo medicines in reference 1). In both mouse and in vitro studies, herbal medicines reportedly affect cytokine secretion, histamine release, immunoglobulin secretion and class switching, cellular coreceptor expression, lymphocyte proliferation, and cytotoxic activity, to name but a few examples (1, 6, 8, 9, 12, 13). Until recently, most studies of the immunomodulatory properties of herbal medicines were published in the Asian-language scientific literature, which is not easily accessible to Western scientists. Today, however, the broader scientific community is beginning to undertake rigorous scientific studies of the immunomodulatory effects of herbal medicines, and Western journals are reporting the results. For example, a recent study with the RET transgenic mouse model of melanoma shows that the anticancer effects of the popular Kampo medicine Juzen-taiho-to are mediated via an enhanced antigen-specific antitumor cytotoxic T-lymphocyte response (3). Many other immunomodulatory properties have been attributed to Juzen-taiho-to, an extract of 10 different plant parts (1). In another recent report, Li et al. (9) use a murine conalbumin challenge model of asthma to show dexamethasone-like effects of MSSM-002, which is derived from the TCM herbal prescription Ja Wai San Zi Tang, a mixture of 14 botanicals commonly used in China to treat asthma. Airway hyperreactivity was eliminated, and lung histology showed reduced inflammation and mucus production compared to sham-treated animals, with results equivalent to those obtained in dexamethasone-treated animals. In contrast to the overall immunosuppressive effects of dexamethasone, herbal treatment decreased antigen-specific immunoglobulin E, as well as interleukin-4 (IL-4), IL-5, and IL-13 secretion from spleen cells, but did not suppress immunoglobulin G2a and gamma interferon synthesis. Intriguing studies like these should encourage further state-of-the-art immunological research on herbal medicines.

Adding further encouragement for such research, more U.S. research dollars are becoming available for the study of traditional herbal medicines. In 1998, the National Institutes of Health established the National Center for Complementary and Alternative Medicine, an expansion of the former Office of Alternative Medicine, with a 2002 research budget of more than \$100 million. The National Center for Complementary

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and Alternative Medicine currently has funded four research centers specializing in botanicals research and lists numerous initiatives to fund training, centers, and research studies of alternative medicine (see <http://nccam.nih.gov/>). In addition, the National Institute of Allergy and Infectious Diseases funds studies of the immunomodulatory properties of herbal medicines and their therapeutic effects on infectious disease. National Institutes of Health institutes with specific disease interests (e.g., the National Cancer Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases) support research on herbal remedies.

Immunologists who undertake the study of herbal medicines will face challenges, as well as opportunities. Almost surely, research into the immunomodulatory properties and mechanisms of action of herbal medicines will provide new insights into immune function and possible avenues of immunotherapy. But such research also will require a fresh perspective and an open mind. In an era of increasingly detailed molecular studies of drug mechanisms, the investigation of the properties of crude herbal extracts may seem a step back in time. A review of recent reports on the immunomodulatory properties of herbal medicines brings to mind early studies on plant lectins like phytohemagglutinin and pokeweed mitogen, wherein one began by collecting plant parts and boiling them to make extracts (2, 5). Not only are herbal medicines minimally processed plant extracts, but the purportedly essential interactions of the components in a given herbal medicine formula make their study even more challenging. The hope is that the excitement of exploring these ancient healing formulas with 21st century science and technology will entice immunologists to rise to the challenge.

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