

Alternative and complementary medicine: A source of improved therapies for asthma? A challenge for redefining the specialty?

Key words: Alternative medicine, asthma

This issue of the *Journal of Allergy and Clinical Immunology* includes an exciting and challenging article exploring the mechanisms of action of a complex herbal formula (MSSM-002) used in the clinical treatment of asthma by the traditional Chinese medicine (TCM) community (p 660). With use of a well-characterized mouse model of allergic asthma, Li et al generate specific and highly significant experimental evidence for an anti-inflammatory, antiasthmatic, and immunomodulating physiologic effect associated with the oral administration of MSSM-002. The anti-inflammatory and anti-airway hyperreactivity effects of MSSM-002 are comparable to those of dexamethasone in this murine model. In contrast to dexamethasone, however, the cytokine profile after antigen challenge plus MSSM-002 is shifted from a T_H2 to a T_H1 pattern with no suppression of IFN- γ or IgG2a production. On the basis of the data, this complex herbal mixture cannot be dismissed as a mere placebo, a fact that is both exciting and threatening for allopathic practitioners and investigators. This courageous study represents a new frontier for clinical research in that the authors, working with an uncharacterized mixture in traditional pharmaceutical terms, tried to faithfully reproduce a mixture that has been clinically used in TCM practice.

MSSM-002 cannot be easily dissected in terms of what active ingredients are responsible for a therapeutic effect. The 14 different herbal extracts in MSSM-002 include several widely hailed asthma-relevant herbals as well as others that are not well referenced in currently available English language resources for herbal medicine.¹⁻⁵ The confusion that can arise with names alone makes cross-referencing articles and references difficult. Mixtures of plant extracts such as MSSM-002 are currently classified as dietary supplements under the "provisions of the Dietary Supplement and Health Education Act of 1994, which prohibits their sale for the diagnosis, treatment, cure, or prevention of any disease."² Yet there are no prohibitions in advertising supplements as aids to help cough,

Abbreviations used

CAM: Complementary or alternative medicine
TCM: Traditional Chinese medicine

cold, or respiratory disease, including asthma. The most recent edition of the *Physician's Desk Reference for Herbal Medicines* (second edition) lists 57 separate "Cough and Cold Products," 2 "Decongestants & Combinations," 23 "Expectorants," and 83 "Respiratory Agents." The German Regulatory Authority's herbal watchdog agency, commonly called "Commission E," has conducted intensive assessments of peer-reviewed literature on some 300 common botanicals, weighing the quality of the clinical evidence and identifying the uses for which an herb can reasonably be considered effective. Of the *Physician's Desk Reference*-listed herbal products, 45 "Respiratory Products" and 22 "Cough and Cold Products" have received a positive recommendation by Commission E. The majority of the ingredients within the MSSM-002 TCM product described in the article are not listed within this most recent "reference" for Western practitioners. The four ingredients specifically listed include *Perilla frutescens* (Zi Su Zi or Su Zi, also an active ingredient of the popular TCM asthma therapy Saiboku-to), *Platycodon grandiflorum* (Jie Gen), *Zingiber officinale* or *Zingiberis rhizoma* (Sheng Jiang or ginger-root), and *Zizyphus jujuba* (Da Zao, in a class with dates and figs).^{2,3} Some of the specific activities noted with each of these ingredients include suppression of IgE production in mice with sedative and antibacterial properties, direct stimulation of the pituitary and hypothalamus with increasing plasma ACTH,⁴ inhibition of both leukotriene and PG synthesis,³ and adaptogenic properties that prevent the immunosuppression of cytotoxic agents.^{2,3} *P frutescens* is specifically noted to be mutagenic in some animal studies.² Reports of inflammatory pneumonitis and alveolitis with Saiboku-to preparations raise concern about adverse effects, especially with long-term use.^{6,7}

Three ingredients were specifically cited in a 1992 National Institutes of Health workshop on alternative medicine report¹: *Glycyrrhiza uralensis* (Gan Cao, associated with inhibition of cortisol-degrading and PGE₂ inactivation enzymes),¹ *Scutellaria baicalensis* (baical skullcap root [Huang Qin, listed as a promising agent for cancer therapy with induction of apoptosis, inhibition of tumor metastasis, and concomitant antibacterial stimulation of the immune system]),¹ and the previously cited *G uralensis*.

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Received for publication July 31, 2000; accepted for publication Aug 1, 2000.

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1/1/110504

doi:10.1067/mai.2000.110504

Boik's classic reference⁴ provides an exhaustive review of herbals with evidence for activity that stimulates or suppresses the immune system or potentially benefits cancer treatment. The following additional ingredients of MSSM-002 are specifically cited: *Angelica sinensis* (Dang Gui, increases IL-2 production in mouse spleen cells and TNF cytotoxicity in mice), *Paeonia lactiflora* (Bai Shao or chi shao, fibrinolytic and inhibition of fibrin production in vitro and tumor metastases), *Prunus armeniaca* (Xing Ren, apricot source, inhibits histamine release, vascular permeability, collagenase and elastinase activity in vitro, scavenges free radicals, and induces cross-linking of collagen); and *Ganoderma lucidum* (Ling Zhi, immune stimulant with inhibition of angiogenesis and histamine release, antitumor activity potential, increased IL-2 and IFN- γ in humans).⁴

Although some attempts are being made by herbal manufacturers to list the quantity of a known active ingredient as one marker of potency, the need for definition of terms or nomenclature as well as specific characterization of plant sources and parts is reminiscent of the earlier days of allergen extracts for allergen immunotherapy. Because by their nature herbal combinations cannot be easily standardized in terms of ingredients like currently licensed Food and Drug Administration–approved drugs can, developing a model and approach to testing complex and relatively crude “food supplement” materials that have achieved public credibility is as important as the specific material in question. It only takes a brief sojourn on the Internet or a visit to your supermarket, corner drug store, health food store, or local bookstore to understand herbal supplements have an impressive market visibility and popular perception of efficacy and safety. A significant component of this outreach into nontraditional healing is directed toward treatment of allergies, asthma, and perceived weaknesses of the immune system. The belief that these supplements are “natural and safe” is widespread although increasing reports of adverse events have raised public awareness that natural is not risk free. For chronic asthma there are real concerns that the use of complementary or alternative medicine (CAM) may delay specific anti-inflammatory therapy and thereby increase risk of emergency visits and hospitalizations.⁸

Li's article makes a significant contribution to CAM integration by providing a template for future testing of other agents that may be marketed as “supplemental” asthma therapies. Although any model has its limitations and the mouse does not necessarily predict responses in man, it is a beginning for establishing credible physiologic evidence that a given preparation may merit further resources to develop or standardize for active ingredients or test in clinical trials. The mechanisms of action of the crude herbal mixture within the mouse asthma model are consistent with our understanding of asthma; this observation is both exciting and supportive of the clinical experience of TCM. The fact that the immune-modulating effect of the mixture was more selective than dexamethasone raises the exciting possibility of a steroid-sparing action and reinforces the possibility that

providers seeing patients with asthma and a history of responding “better” to some nontraditional medicines may be dealing with more than a “placebo” effect. The article strengthens the need for a change in attitude within the medical profession to recognize the fact that medically efficacious therapies, from the patient's perspective, may come from arenas other than traditional allopathic medicine and pharmaceuticals.

Although practitioners of allopathic or scientifically based medicine have dominated traditional Western medicine, there are increasing forces within the American culture demanding the inclusion of CAM in therapeutic choices. Many traditional practitioners of medicine, including mainstream allergy-immunologists, are bewildered as to why the American public aggressively seeks out CAM for their medical problems. The facts that these therapeutic alternatives have ill-defined risk profiles and involve out-of-pocket expense at a time when the concerns about cost containment are at an all-time high are a further confusion to many.⁹ At the same time, patients are seeking support and guidance from their traditional health care provider with encouragement from most “supplemental therapies” to consult their physicians. How do we prepare ourselves to partner effectively and safely? What are the liability concerns?¹⁰ Eisenberg¹¹ provides a commonsense step-by-step strategy for those providers who would become part of the health care team with alternative practitioners.

The scope of what is included in the array of CAM treatments can be overwhelming to the health care providers trying to learn about them. Herbal medicine alone encompasses several textbooks of information but with no well-defined “evidence-based” guidelines or easily accessed educational material. Most physicians complain of difficulty remaining current with the knowledge required for the practice of allopathic medicine. Therapeutic arenas such as herbal medicine (with more than 1800 herbals currently available on the US market) are overwhelming in informational content.¹² It has been easier to ignore the whole area of CAM as “placebo” or “not effective” and many patients complain that it is difficult to find a health care provider willing to partner with alternative practitioners or to monitor them if they choose an herbal or other CAM therapeutic trial outside the Food and Drug Administration–approved pharmaceutical industry. There is a need for balanced educational opportunities¹³ and consensus guideline development to arm physicians with the requisite skills to provide review of efficacy for a given patient balanced against the risks of adverse reactions or herb-drug interactions. It will be increasingly difficult to provide care for allergic and asthmatic patients without some understanding of herbal medicine.¹⁴ The future role of allergy-immunology in this arena is potentially an exciting one, challenging everyone within the specialty.

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