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File: ■ Andrographis (*Andrographis paniculata*)

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RE: Pharmacology and Clinical Effects of Andrographis

Akbar S. *Andrographis paniculata*: a review of pharmacological activities and clinical effects. *Altern Med Rev*. 2011;16(1):66-77.

Andrographis (*Andrographis paniculata*) is widely used in Unani and Ayurveda, traditional medicine systems of India. It is also a traditional medicine in China, Hong Kong, the Philippines, Malaysia, Indonesia, and Thailand. Aerial parts are most used, but the whole plant or roots also have some uses. Traditional administration is by infusions, decoctions, or powders, alone or with other herbs. Juice is given to infants with loose bowels or poor appetite. Leaves and root are used to treat general debility, dyspepsia, and advanced dysentery. Modern commercial preparations are usually standardized extracts. Andrographis' bioactive compounds include lactones, diterpenoids, diterpene glycosides, flavonoids, flavonoid glycosides, alkanes, ketones, and aldehydes. The leaves have two bitter principles, andrographolide and kalmeghin.

Many conditions traditionally treated with andrographis are self-limiting. Unani considers it aperient, anti-inflammatory, emollient, astringent, diuretic, emmenagogic, carminative, tonic, antihelmintic, and antipyretic. It is said to "purify" the blood. In China, it is considered bitter, cold, antipyretic, detoxicant, anti-inflammatory, and detumescent, "reducing blood heat." It is currently reported to have antibacterial, antifungal, antiviral, choleretic, hypoglycemic, hypercholesterolemic, and adaptogenic effects.

Indian systems of medicine use andrographis to stimulate and protect the liver, alone or in multiherb preparations. One of the latter has been reported effective against chronic hepatitis B virus. Few studies have used crude andrographis extracts. Most have used andrographolide or other possible active constituents. Hepatoprotective effects have been consistently reported. Animal studies have found andrographolide as protective or more protective than silymarin from milk thistle (*Silybum marianum*) against numerous hepatic injuries, e.g., acetaminophen-, ethanol-, and carbon tetrachloride (CCl_4)-induced. Against the last, the crude extract was more effective than andrographolide alone, indicating more than one hepatoprotective compound. One study compared andrographolide, a methanol whole-plant extract with an equal amount of andrographolide, and an andrographolide-free methane extract against CCl_4-induced liver damage; all three improved rat liver histology. Andrographis' activity against agents

with different hepatotoxic mechanisms suggests broad hepatoprotectivity. Large, multi-center clinical studies are warranted.

A few studies have examined andrographis' effects on hepatic metabolic enzymes. While it seems clear that the plant and/or its compounds are metabolically active, variously inducing or inhibiting select microsomes, the evidence is insufficient to draw conclusions about potential herb-drug interactions. Studies are needed in healthy humans and in those using medicines that may be pharmacokinetically altered (See Peer Reviewer's Note 1).

Andrographis preparations have been used with good results reported for infectious and non-infectious conditions from epidemic Japanese B encephalitis to viper bites. Chinese studies report benefits in bacillary dysentery and gastroenteritis with cure rates better than those of furazolidone or chloramphenicol. Andrographis has been tested against some bacteria, viruses, and parasites. Crude powder lacked antibacterial action. Aqueous extracts showed substantial antibacterial activity, perhaps attributable to the combined effects of andrographolide and arabinogalactan protein. Andrographolide, neoandrographolide, and 14-deoxy-11,12-didehydroandrographolide (DDA) are all active against herpes simplex virus 1. An alcohol rhizome extract was active against malarial parasite *Ascaris lumbricoides*, halting in vitro growth within 24 hours. A methanol extract significantly inhibited *Plasmodium falciparum*, as did four xanthones from andrographis root. These xanthones also inhibited *P. berghei* in vivo, and *Trypanosoma brucei*, *T. cruzi*, and *Leishmania infantum*.

Clinical studies have concentrated on upper respiratory tract infections (URTIs) with most finding andrographis safe and effective against symptoms (See Peer Reviewer's Note 2). Two systematic reviews also found it safe and effective for simple URTIs compared to placebo. Kan Jang, combining andrographis and eleuthero (*Eleutherococcus senticosus*), tested in two parallel group randomized, double-blind, placebo-controlled trials (RCTs) in Sweden, produced highly significant throat symptom relief in both compared to placebo. An Armenian RCT found significant improvement in other symptoms. In a Thai RCT, efficacy was comparable to acetaminophen. A major modern use of andrographis is to prevent and treat the common cold. A three-armed RCT compared standard cold treatment, standard treatment with Kan Jang, and standard treatment with echinacea (*Echinacea* spp.) in children 4-11 years of age. Those receiving Kan Jang had less severe symptoms, faster recovery, and needed significantly less standard medication.

Andrographis appears to be anti-thrombotic and may have benefits in cardiovascular disease. An aqueous root extract dose-dependently decreased systolic blood pressure in vivo. Another extract significantly inhibited ex vivo platelet aggregation in 63 patients with cardio- or cerebrovascular diseases in three hours, with even more significant benefits at one week. Further study is needed of andrographis' potential uses as suggested by pharmacological studies, such as for myocardial infarction, ischemia, and after balloon angioplasty. Similarly, several significant antihyperglycemic effects in diabetic rats with both water and alcohol extracts demand further study. Improved glucose utilization and increased insulin release have been proposed as mechanisms of action.

—Mariann Garner-Wizard

Peer Reviewer's Note 1:
It should be mentioned that the results of in vitro studies on isolated cells (which are valuable when the mechanisms behind the estimated pharmacological activity are studied) could not have any clinical significance. Direct pharmacokinetic studies of drugs sensitive to cytochrome P450 (CYP) enzymes provide more convincing evidence regarding possible drug-herb interactions, when they are applied concomitantly. Such a possibility of an interaction between warfarin and Kan Jang (a combination of *Andrographis paniculata* and *Eleutherococcus senticosus*) has been studied in rats [Hovhannisyan et al., 2006].[1] The authors found that Kan Jang had no significant influence on the pharmacokinetics and pharmacodynamics of warfarin, indicating there should also be no interactions of Kan Jang with other drugs sensitive to CYP1A2, CYP2C9, and CYP3A4 enzymes (CYPs predominantly used in metabolism of warfarin). Each day for 5 days, 2 groups of rats (n = 54) were given an oral dose of Kan Jang (equivalent to 17 mg/kg andrographolide) or water. Sixty minutes after dosing, the animals were administered 2 mg/kg warfarin and at 0, 2, 4, 6, 8, 12, 24, 30, and 48 hours after that 6 animals from each group were sacrificed, blood samples taken, and the concentration of warfarin was measured by high-performance liquid chromatography (HPLC). The concentration of warfarin in the Kan Jang treatment group was slightly higher than in the control group during the first 6-7 hours following administration and attained its maximum value earlier than control. However, the mean C_{max} values, elimination half-life, and mean residence time between the two groups were not statistically significant. Prothombin time (PT) measurements (mean PT_{max} and $AUC_{PT\ 0-\infty}$ [area under the concentration-time curve]) were not statistically different between the two groups.

In a similar study, extremely high doses of *Andrographis paniculata* extract (APE) (1 and 2 g/kg of rats' body weight) and its major component, andrographolide (AG) (77 and 154 mg/kg), were investigated on the pharmacokinetics of theophylline (a substrate of CYP1A2 enzyme) [Chien et al., 2010].[2] The results indicated that the clearance of theophylline was significantly increased and the AUC was reduced in both AG and APE pretreated groups at low-dose theophylline administration (1 mg/kg). The authors suggest that patients who want to use CYP1A2-metabolized drugs such as caffeine and theophylline should be advised of the potential herb-drug interaction [Chien et al., 2010].[2] However, this precaution is based on the assumption that patients have to take andrographis in doses at least 10-20 times higher than it is normally prescribed for the treatment of common cold. The daily dose of andrographolide in humans is about 1 mg/kg of body weight.

Peer Reviewer's Note 2:
The results of a literature search of **CLINICAL EFFICACY OF ANDROGRAPHIS IN THE TREATMENT OF ACUTE UPPER RESPIRATORY TRACT INFECTIONS** using MEDLINE, PubMed, Iowa Drug Information System, International Pharmaceutical Abstracts, the Cochrane Library Database, MICROMEDEX, and the Natural Medicines Comprehensive Database:

- *Andrographis paniculata* in individual preparations – only 3 studies (two RCTs and one nonrandomized trial),
- Kan Jang fixed combination of *Andrographis paniculata* and *Eleutherococcus senticosus* – 12 studies (ten RCTs and two nonrandomized trials).

References

[1]Hovhannisyan AS, Abrahamyan H, Gabrielyan ES, Panossian AG. The effect of Kan Jang extract on the pharmacokinetics and pharmacodynamics of warfarin in rats. *Phytomedicine*. 2006;13(5):318-323.

[2]Chien CF, Wu YT, Lee WC, Lin LC, Tsai TH. Herb-drug interaction of *Andrographis paniculata* extract and andrographolide on the pharmacokinetics of theophylline in rats. *Chem Biol Interact*. 2010;184(3):458-465.

Referenced article is available at http://www.altmedrev.com/publications/16/1/66.pdf.