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Andrographis paniculata in the Treatment of Upper Respiratory Tract Infections: A Systematic Review of Safety and Efficacy

Abstract

Acute respiratory infections represent a significant cause of overprescription of antibiotics and are one of the major reasons for absence from work. The leaves of *Andrographis paniculata* (Burm.f.) Wall ex Nees (Acanthaceae) are used as a medicinal herb in the treatment of infectious diseases. Systematic literature searches were conducted in six computerised databases and the reference lists of all papers located were checked for further relevant publications. Information was also requested from manufacturers, the spontaneous reporting schemes of the World Health Organisation and national drug safety bodies. No language restrictions were imposed. Seven double-blind, controlled trials (n = 896) met the inclusion criteria for evaluation of efficacy. All trials scored at least three, out of a maximum of five, for methodological quality on the Jadad scale. Collectively, the data suggest that *A. paniculata* is superior to placebo in alleviating the subjective symptoms of uncomplicated upper respiratory tract infection. There is also preliminary evidence of a preventative effect. Adverse events reported following administration of *A. paniculata* were generally mild and infrequent. There were few spontaneous reports of adverse events. *A. paniculata* may be a safe and efficacious treatment for the relief of symptoms of uncomplicated upper respiratory tract infection; more research is warranted.

Key words
Medicinal plants · herbal medicine · upper respiratory infections · systematic review · *Andrographis paniculata* · Acanthaceae

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Introduction

In the UK, an acute respiratory infection is the commonest reason for a patient to consult a general practitioner. Thirty million courses of antibiotics are prescribed per year for the treatment of acute respiratory infections [1], despite evidence that they neither shorten the course of acute viral infections nor prevent secondary bacterial infections [2]. The overuse of antimicrobial drugs for the management of respiratory infections has important implications for healthcare costs and the potential for emergence of antimicrobial resistance [3].

In light of the continued popularity of herbal medicine [4], an effective and well-tolerated herbal medication for the prevention and treatment of acute respiratory infections would be a welcome addition to the therapeutic repertoire. The leaves of *Andrographis paniculatam*, popular in Scandinavia as a cold and influenza remedy, are used traditionally in Ayurvedic, Thai and Chinese medicine to treat fever associated with infectious diseases. Pharmacological studies suggest anti-inflammatory [5], [6], antipyretic [7], [8], antiviral [9] and immunostimulatory [10] properties. The aim of this review was to systematically assess the efficacy and safety of *A. paniculata* in the treatment and prevention of upper respiratory tract infections.

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Received September 22, 2003 · **Accepted** January 10, 2004

Bibliography
Planta Med 2004; 70: 293–298 · © Georg Thieme Verlag Stuttgart · New York · ISSN 0032-0943 · DOI 10.1055/s-2004-818938

Methods

Identification of clinical trials

In order to identify all reports of administration of *Andrographis paniculata* to human subjects, systematic literature searches were conducted in the following electronic databases: Medline (Via Pubmed), Embase, CINAHL, Amed (Alternative and Allied Medicine Database, British Library Medical Information Centre), The Cochrane Library (Issue 2, 2003), and the British Library Index of Conference Proceedings (all from their inception to June 2003). The search terms used were: *Andrographis paniculata*, kalmegh, kiryat, chuanxinlian, chiretta, fa-tha-lai-jone and Kan Jang. Further relevant papers were located by hand-searching the reference lists of all papers and departmental files. Hand searching of standard reference texts [11], [12] and internet searches revealed four manufacturers/distributors of *A. paniculata* products who were contacted and asked to supply any published or unpublished material.

Adverse event reports

Data were requested from the following spontaneous reporting schemes: the World Health Organisation (Uppsala Monitoring Centre), and the drug safety bodies of the United Kingdom (Medicines Control Agency), Australia (Adverse Drug Reactions Advisory Committee) and Germany (Bundesinstitut für Arzneimittel und Medizinprodukte).

Inclusion and exclusion criteria

For the evaluation of efficacy, only double-blind, controlled clinical trials of the oral administration of single or combination preparations of *A. paniculata* for the treatment of uncomplicated upper respiratory tract infection (URTI) were included. All retrieved data including uncontrolled trials, case reports, pre-clinical and observational studies and clinical trials for other indications were included in the review of safety. No language restrictions were imposed.

Data extraction and quality assessment

All articles were read in full. Data relating to sample size, study design, intervention and control, treatment duration, primary outcome measures, number and type of adverse events and results were extracted according to predefined criteria. The methodological quality of each clinical trial was assessed using the Jadad scoring system [13]; a scale ranging from 0 (poorest) to 5 (highest) which assesses methods of randomisation and blinding and the description of withdrawals and dropouts.

Study selection, data extraction and assessment of methodological quality were performed by the first reviewer and validated by the second, with any disagreements being settled by discussion.

Results

A total of 143 references were retrieved from the systematic literature searches; eleven papers described the administration of *A. paniculata* to human subjects. These included four double-blind, controlled clinical trials of the treatment of uncomplicated URTI (three further eligible trials were identified from reference lists and our own departmental files) (Table **1**) [14], [15], [16], [17], [18], a phase I trial in HIV positive and negative patients [20], two studies in healthy volunteers [21], [22], and three case series [23], [24], [25]. Adverse events reported within these twelve papers are shown in Table **2**.

Evaluation of efficacy

Seven double-blind, controlled trials (n = 896) met the inclusion criteria [14], [15], [16], [17], [18], [19]. Of these, five were randomised and six were placebo-controlled; one compared the effects of *Andrographis paniculata* with paracetamol. All trials scored at least three out of five points for methodological quality.

Melchior et al. in 2000 conducted two randomised, double-blind, placebo-controlled parallel group clinical trials of a fixed combination of standardised extracts of the leaves of *A. paniculata* (60 mg andrographolide/day) and the roots of *Eleutherococcus senticosus* (Rupr. & Maxim) Maxim (120 mg/day) in 47 and 180 adult patients with uncomplicated acute URTI treated within 36 hours of the onset of symptoms [18]. Primary outcome measures were patient and physician evaluation of the severity of pre-defined signs and symptoms (e.g., muscle pain, cough, throat, nasal and eye signs and symptoms and temperature). In the larger study, there was a significantly greater improvement in both patient ($p = 0.0006$) and physician ($p = 0.003$) evaluated total symptom scores in the treatment group compared with placebo, after three days. Analysis of individual symptoms showed significant differences in muscle soreness, cough frequency, presence of a productive cough, body temperature and dry throat. The smaller, pilot study showed a non-significant reduction in patient evaluated total symptom score in the treated group, compared with placebo ($p = 0.08$). Physician symptom evaluation was not reported.

Two hundred men and women with a diagnosis of upper respiratory tract infection (not requiring treatment with antibiotics) were treated with either a fixed combination of *A. paniculata* (60 mg andrographolide/day) and *E. senticosus* (120 mg/day) or placebo for five days in a non-randomised, double-blind, parallel group study performed in two centres in the Republic of Armenia [15]. Clinical observations included evaluation of the following signs and symptoms, rhinitis, sinusitis, pharyngitis, fever, abnormal pulmonary findings, lymphadenopathy, nasal discharge and stuffiness, sore throat, earache, cough and headache. Although there was a significant difference in mean symptom scores between groups at baseline (treatment 0.65 vs. placebo 0.82; $p = 0.006$) there was also a highly significant difference at the end of treatment (treatment 0.09 vs. placebo 0.63; $p < 0.001$). Subsequent statistical analyses suggest that although the baseline mean score affected the mean score post-treatment, it did not interfere with the observed difference in improvement between the two groups. The baseline difference was thought to be due to differences in the type of patients recruited at the two centres; one of which was an emergency department and the other an outpatient clinic. Headache, nasal and throat symptoms and general malaise showed the most improvement, whilst cough and eye symptoms did not differ between the groups.

In a randomised, placebo-controlled double-blind study of 208 adult patients diagnosed with uncomplicated URTI (ICPC classification), Caceres et al. collected patient self-evaluations of head-

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Table **1** Double-blind, controlled trials of *Andrographis paniculata* for the treatment of uncomplicated URTI

First author (reference)	*Quality score*	*N (randomised/ analysed)*	*Study design*	*Type of preparation*	*Daily dose of andrographolide (mg)*	*Duration (days)*	*Delay between onset of symptoms and start of therapy (hours)*	*Main results*
Melchior [18]	5	47/46	R, PC, treatment	standardised extract; AP/ES combination	60	3 – 8	36	greater improvement in patient's overall symptom score compared with placebo ($p = 0.08$)
Melchior [18]	5	180/179	R, PC, treatment	standardised extract; AP/ES combination	60	3	36	greater improvement in patient's ($p = 0.0006$) and physician's ($p = 0.003$) overall symptom score compared with placebo
Gabrielian [15]	3	200/185	PC, treatment	standardised extract; AP/ES combination	60	5	N/A	greater improvement in mean symptom score compared with placebo at day 5 ($p < 0.001$)
Caceres [14]	5	208/208	R, PC, treatment	standardised extract	60	5	48	improvements in all symptoms compared with placebo ($p < 0.03$)
Melchior [17]	3	50/50	R, PC, treatment	standardised extract	60	5	72	fewer days sick leave compared with placebo after five days ($p < 0.03$)
Hancke [16]	3	59/59	PC, treatment	standardised extract	48	5	72	decrease in summary scores for signs ($p < 0.05$) and symptoms ($p < 0.01$) compared with placebo after four days
Thamlikitkul [19]	3	152/142	R, C, treatment	crude drug (high or low dose) or paracetamol	180 or 360	7	not known	greater eradication of sore throat and fever in high dose and paracetamol groups compared with the low dose group after three days ($p < 0.001$). No differences between groups after seven days

R = randomised; PC = placebo controlled; C = comparative.

ache, fatigue, earache, sleep disturbance, soreness of throat, nasal secretion, expectoration and frequency and intensity of cough on a visual analogue scale, within 48 hours of the onset of symptoms and after two and four days of treatment with either *A. paniculata* (60 mg andrographolide/day) or placebo [14]. Compared with placebo, fatigue, sleep disturbance, nasal secretion and soreness of throat ($p < 0.03$) were all improved after two days of treatment; on day four there were significantly greater improvements in all symptoms (all $p < 0.01$).

Fifty adult patients with uncomplicated URTI received a standardised extract of *A. paniculata* (andrographolide 60 mg/day) or placebo within 72 hours of the onset of symptoms in a randomised, double-blind, placebo-controlled trial [17]. Although the primary outcome measures were patient- and physician-evaluated symptom scores, these are not reported, instead the results are presented as several summary measures. After five days of treatment, there was a significant difference between groups in the number of sick leave days reported and the number of patients who declared themselves 'totally recovered' (0.96 vs. 0.21; $p < 0.03$ and 67.5 vs. 36 %; $p < 0.046$).

Hancke et al. conducted a non-randomised, placebo-controlled double-blind study of 59 adult patients diagnosed with common cold [16]. Within 72 hours of the onset of symptoms, patients received treatment with either a standardised extract of *A. paniculata* (andrographolide 48 mg/day) or placebo for five days. After four days of treatment there was a decrease in summary scores for signs ($p < 0.05$) and symptoms ($p < 0.01$) compared with placebo. Both groups showed significant reductions in shivering, sore throat and muscular ache; in addition, treatment with *A. paniculata* was associated with reductions in the strength of the disease, tiredness, rhinitis, sinus pains and headaches.

In a comparative study, 152 patients with sore throat and either a history of fever or a temperature of at least 37.8 °C were randomised to receive encapsulated dried leaves of *A. paniculata* (andrographolide 180 or 360 mg/day) or paracetamol (3.9 g/day) for seven days [19]. The study medications were prepared in identical capsules. There was a significant difference in efficacy in favour of paracetamol and high dose *A. paniculata* for eradication of sore throat and fever at day three ($p < 0.001$). By day seven there were no significant differences between the groups with almost all patients being symptom-free.

Evaluation of safety

Spontaneous reporting schemes: As of June 2003, no reports of suspected adverse events associated with *A. paniculata* had been received by the national drug safety bodies of the United Kingdom, Germany or Australia. The World Health Organisation Collaborating Centre for International Drug Monitoring provided three reports of anaphylactic shock [1 report] and anaphylactic reaction [2 reports]. All occurred in Sweden in 1996, no further

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Table **2** Adverse events reported during administration of *Andrographis paniculata* to human subjects

First author (reference)	*N*	*Patient population*	*Study design*	*Daily dose of andrographolide (mg)*	*Adverse events experienced (cases)*	
					Active treatment	*Placebo*
Melchior [18]	47	URTI	R, DB, PC	60	no adverse events reported	no adverse events reported
Melchior [18]	180	URTI	R, DB, PC	60	unpleasant sensations in the chest (1), intensified headache (1)	no adverse events reported
Gabrielian [15]	200	URTI	DB, PC	60	increased nasal discharge and epigastric pain (1), blocked nose (1), severe headache (1)	no adverse events reported
Calabrese [20]	18	HIV positive (13) and healthy volunteers (5)	O	5 mg/kg and 10 mg/kg increasing every 3 weeks	allergic reaction (2), fatigue (6), headache (5), pruritis/rash (12), diarrhoea (5), nausea (1), metallic taste (6), bitter taste (2), decreased/no taste (6), dry tongue (1), decreased sex drive (1), eyes sensitive to light (1), decreased short term memory (1), dizziness (1), heartburn (1), tender lymph nodes (3), lymphadenopathy (2)	no placebo group
Panossian [21]	16	healthy volunteers	O, SD, R	20	no adverse events reported	no adverse events reported
Caceres [14]	208	URTI	R, DB, PC	60	no adverse event information provided	no adverse event information provided
Caceres [35]	107	healthy students	R, DB, PC	11	no adverse event information provided; no withdrawals	no adverse event information provided; no withdrawals
Melchior [17]	50	URTI	R, DB, PC	60	urticaria (2)	no adverse events reported
Muangman [24]	100	patients with renal stones	case series	40	no adverse events reported	no placebo group
Hancke [16]	59	URTI	PC, DB	48	no adverse events reported	no adverse events reported
Zhang [23]	63	patients with cardiac and cerebral vascular disease	case series	various	no adverse events reported	no placebo group
Thamlikitul [19]	152	sore throat and fever	R, DB, C	180 or 360 mg or paracetamol	adverse events were experienced by approx. 20% of patients in each group and included nausea, vomiting, abdominal discomfort, dizziness, drowsiness and malaise	no placebo group
Leelarasamee [22]	10	healthy volunteers	SD, R, CO	not known	no adverse event information provided	no adverse event information provided
Vedavathy [25]	25	children with infective hepatitis	case report	not known	no adverse event information provided	no adverse event information provided

R = randomised; O = open; DB = double-blind; PC = placebo-controlled; SD - single dose.

reports had been received. The World Health Organisation states that the information provided is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction and that the information does not represent the opinion of the World Health Organisation.

Data from manufacturers: Information was received from one of the four manufacturers/distributors of *Andrographis paniculata* products contacted; the Swedish Herbal Institute. As of 1981, they had received five reports of adverse events (allergic reactions). No further information was available.

Clinical trials and case series: Adverse events were reported in five of the thirteen clinical trials identified. A phase I trial of HIV-positive patients and healthy volunteers, was terminated early due to the large number of adverse events [20]. A contributing factor may have been the dose of andrographolide used (5 – 10 mg/kg/day) which was in the region of six to twelve times higher than that used in all the other studies (e.g., 60 mg/day). Adverse events reported in the remaining trials were mild, infrequent and reversible. In three trials no adverse events were experienced by any of the patients in either the treated or placebo groups and the remaining three reports contained no informa-

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tion regarding adverse events. No adverse events were reported in any of the case series

Experimental studies: Several animal studies were identified which suggest that *A. paniculata* may have contraceptive or antifertility effects following long-term treatment at high doses [26], [27], [28]. However, there is a large degree of discrepancy in the results, with some studies [29], [30] demonstrating no untoward effects even at doses 1000 times those used therapeutically, possibly due to the type of extracts used and the techniques employed to detect change. More work is needed in this area, but the evidence to date suggests that *A. paniculata* should not be taken during pregnancy or by men or women attempting to achieve conception.

Discussion

A paniculata alone or in combination with *E. senticosus* appears promising in the treatment of subjective symptoms of uncomplicated upper respiratory tract infection. Short-term therapy at recommended doses is associated with an encouraging safety profile, although adverse events have been demonstrated at higher doses.

This review represents the first attempt to systematically collate the available data on *A. paniculata*, in many countries a relatively unknown and little studied herb, in an area of medicine in which most current conventional treatment options are largely ineffective. The trials included within the review were large, well designed and of good to excellent methodological quality, and the safety data represent all available information surrounding the incidence of adverse events following administration of *A. paniculata*. We were unable to formally combine the data from individual trials in a meta-analysis as the most appropriate primary outcome measure, sum score for patient-reported symptoms, was available for only four of the trials, and attempts to retrieve this data for the remaining trials from the manufacturer/authors were unsuccessful.

Several shortcomings of the review need to be addressed. Firstly, with the exception of Thamlikitkul et al. [19], all the trials involved a standardised extract of *A. paniculata* manufactured by the same herbal company, a representative of whom is a co-author on each of the papers. Pooling a relatively small number of trials of this nature may be prone to error and potential bias. Secondly, although attempts were made to obtain data from unpublished trials by contacting authors/manufacturers and searching the Index of Conference Proceedings, none were located. There is evidence to suggest that studies with significant positive results are more likely to be published [31] and this may be more pronounced with an unfamiliar therapy such as *A. paniculata*. Finally, the safety data should be interpreted with some degree of caution. Generally, adverse events experienced during clinical trials were mild and infrequent, however, trials designed to assess efficacy rarely collect rigorous information on adverse events. Typically each trial includes a relatively small number of patients exposed for a short period of time thus reducing the possibility of observing rare or delayed adverse events. There have also been very few adverse events reported to the various surveillance bodies and manufacturers. There is evidence that patients do not report all adverse events experienced after taking over-the-counter medications whether herbal or conventional [32] and that hospital doctors under-report adverse events [33]. We do not have any figures for the number of patients exposed to *A. paniculata* and the lack of reports could indicate a lack of awareness or availability of the herb. On the other hand, the Australian surveillance body reported that *Andrographis paniculata* was present in 22 of the products listed on the Australian Register of Therapeutic Goods; none of which was associated with reports of adverse events.

Studies *in vitro* suggest that *A. paniculata* may have several potential mechanisms of action relevant in the treatment of acute upper respiratory tract infections including anti-inflammatory [5], [6], [34], immunostimulant [10] and anti-pyretic effects [7], [8]. Although, *A. paniculata* has been reported to inhibit viral replication in HIV infected cells [20], there are no published data of similar effects with respiratory viruses. As viral replication in the upper respiratory tract is believed to peak on the first day of symptoms, it is unlikely in these trials, where treatment was initiated 36 to 72 hours after the onset of symptoms, that an antiviral mechanism of action was involved.

In conclusion, these data suggest that *A. paniculata* may be a promising treatment for the alleviation of subjective symptoms of acute upper respiratory tract infection. In addition, short-term treatment, at recommended doses, is associated with few reports of adverse events. In light of the lack of effective therapeutic options for acute upper respiratory tract infection, *A paniculata* is a herbal treatment option that is worthy of consideration for further research.

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Acknowledgements

JTC was supported by a research fellowship provided by Pharmaton SA, Lugano, Switzerland.

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