

Pharmacological Aspects of *Andrographis paniculata* on Health and Its Major Diterpenoid Constituent Andrographolide

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Nowadays, research on medicinal plants has attracted a lot of attention globally. A number of evidence has been accumulated to demonstrate promising potential of medicinal plants used in various traditional, complementary, and alternative systems. In recent years, a medicinal plant, *Andrographis paniculata*, and its major active phytochemicals have been extensively studied for several pharmacological activities. To understand the mechanism of action, researches have to be carried out at molecular levels. The present review aims at compiling consequential compendium of pharmacological benefits of health on this plant and its major diterpenoid constituent andrographolide that have been tested in various experimental models using modern scientific methodologies.

Key words — *Andrographis paniculata*, andrographolide, diterpenoid, pharmacological potential

INTRODUCTION

An herb is a plant or plant part used for its scent, flavor, or therapeutic properties, and medicinal products made of them are frequently taken to improve health as dietary supplements. Herbs are usually eaten for a long time in combinations, in relatively large, unmeasured quantities under folklore remedies. Therefore, the real challenge lies not in proving whether herbs have health benefits, but in defining what these benefits are and developing the methods to expose them by scientific means.¹⁾

Andrographis paniculata (Burm.f.) Nees is an herbaceous plant, commonly known as “King of Bitters,” in the family Acanthaceae. It is widely cultivated in southern Asia. Mostly the leaves and roots have been traditionally used over the centuries for different medicinal purposes in Asia and Europe as a folklore remedy for a wide spectrum of ailments or as an herbal supplement for health promotion (Table 1). The *Indian Pharmacopoeia* nar-

rates that it is a predominant constituent of at least 26 Ayurvedic formulations.^{2,3)} In traditional Chinese medicine, it is an important “cold property” herb used to rid the body of heat, as in fevers, and to dispel toxins from the body.⁴⁾ In Scandinavian countries, it is commonly used to prevent and treat the common cold.⁵⁾ In Thailand, this plant was selected by the Ministry of Public Health as one of the medicinal plants to be included in “The National List of Essential Drugs A.D. 1999” (List of Herbal Medicinal Products).⁶⁾ Extensive research has revealed that *Andrographis paniculata* has a surprisingly broad range of pharmacological effects and some of them are extremely beneficial, such as anti-inflammatory,^{7–11)} anti-diarrhoeal,^{12,13)} antiviral,¹⁴⁾ anti-malarial,^{15,16)} hepatoprotective,^{17–29)} cardiovascular,^{30,31)} anticancer,^{32–39)} and immunostimulatory^{40–44)} activities. On the other hand, male reproductive toxicity⁴⁵⁾ and cytotoxicity⁴⁶⁾ of this plant have been reported as well.

MORPHOLOGY, CHEMISTRY AND BIOTRANSFORMATION

Andrographis paniculata is an annual herb, ex-

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Table 1. The Traditional Uses of *Andrographis paniculata*^{2-6,47,51,59,76)}

	Native Names	Traditional Uses
Traditional Chinese Medicine (TCM)	Chuan-Xin-Lian	Fever, Common cold
	Chunlianqialio	Laryngitis, Pharyngitis, Tonsillitis
	Yiqianxi	Pneumonia
	Si-Fang-Lian	Respiratory infections
	Zhanshejian	Hepatitis
Traditional Indian Medicine	Kalmegh	Diabetes
	Kiryato	Dysentery, Enteritis
	Maha-tikta	Helminth infection
	Bhunimba	Herpes
		Peptic ulcer
Traditional Thai Medicine	Fah Tha Lai	Fever, Common cold
	Nam Rai Pangpond	Non-infectious diarrhea
		Snake-bites (topical use)
Malaysia	Hempedubumi	Diabetes
	Sambiloto	Hypertension
Japan	Senshinren	Fever, Common cold
Scandinavian	Green Chiretta	Fever, Common cold

**Fig. 1.** Morphology of *Andrographis paniculata*

tremely bitter in taste in every part of the plant body. It grows erect to a height of 30–110 cm in moist shady places with glabrous leaves and white flowers with rose-purple spots on the petals. The stem dark green, 0.3–1.0 m in height, 2–6 mm in diameter, quadrangular with longitudinal furrows and wings on the angles of the younger parts, slightly enlarged at the nodes; leaves glabrous, up to 8.0 cm long and 2.5 cm broad, lanceolate, pinnate; flowers small, in lax spreading axillary and terminal racemes or pan-

icles; capsules linear-oblong, acute at both ends, 1.9 cm × 0.3 cm; seeds numerous, sub quadrate, yellowish brown (Fig. 1). It grows abundantly in south-eastern Asia, *i.e.*, India, Sri Lanka, Pakistan, Java, Malaysia, and Indonesia, while it cultivated extensively in India, China, and Thailand.^{2,47)}

The aerial parts of the plant (leaves and stems) are used to extract the active phytochemicals. Previous investigations on the chemical composition of *Andrographis paniculata* showed that it is

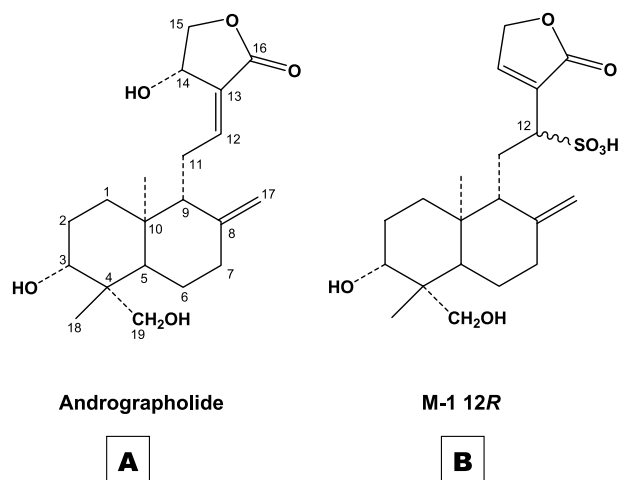


Fig. 2. Chemical Structures of Andrographolide⁵²⁾ and 14-deoxy-12(*R*)-sulfo-andrographolide⁵⁴⁾

Table 2. Pharmacological Potentials of *Andrographis paniculata*

Pharmacological benefits	References
Hepatoprotective activity	17, 18–25, 27–29
Immunological benefits	14, 33–43, 59–65
Anti-inflammatory activity	4, 7–11, 44, 62, 66–72
Respiratory system benefits	5, 73–75
Antimalarial activity	15, 16, 20
Antidiarrheal and intestinal effects	12, 13, 76
Cardiovascular activity	30, 31, 77–80
Psycho-pharmacological activity	81, 82
Hypoglycemic activity	83
Anti-fertility activity	45, 84–88

a rich source of diterpenoids and 2'-oxygenated flavonoids including andrographolide, neoandrographolide, 14-deoxy-11,12-didehydroandrographolide, 14-deoxyandrographolide, isoandrographolide, and 14-deoxyandrographolide 19 β -D-glucoside, homoandrographolide, andrographan, andrographosterin, and stigmasterol.^{6,48,49)} The primary bioactive component of the medicinal plant *Andrographis paniculata* is andrographolide.^{49–51)} Andrographolide [C₂₀H₃₀O₅; (3-[2-{decahydro-6-hydroxy-5-(hydroxymethyl)-5,8 α -dimethyl-2-methylene-1-naphthalenyl}ethylidene]dihydro-4-hydroxy-2(3H)-furanone); Fig. 2A] is a colorless crystalline bicyclic diterpenoid lactone and has a very bitter taste.⁵²⁾ It presents in all parts of the plant, maximally in the leaves (> 2%).

When orally consumed, andrographolide appears to accumulate in organs throughout the viscera. Pharmacokinetic studies showed that andro-

grapholide is quickly absorbed and extensively metabolized in rats and humans.⁵³⁾ Ninety percent is eliminated within 48 hr. Andrographolide metabolites are mainly identified as sulfonic acid adducts and sulfate compounds, as well as glucuronide conjugations. Ten metabolites of andrographolide as sulfonates, sulfate ester compounds, and andrographolide analogues were isolated from rat urine, feces, and the contents of the small intestine after the drug was orally administered to rats,^{54–56)} while those metabolites isolated from human urine were as sulfates, cysteine S-conjugate, and glucuronide conjugates.^{52,57)} One of the metabolites, 14-deoxy-12(*R*)-sulfo-andrographolide (M-1 12R, Fig. 2B) was reported to be identical to the anti-inflammatory drug, Lian-bi-zhi, which is being clinically used in China.⁵⁸⁾

PHARMACOLOGICAL POTENTIAL

Hepatoprotective Activity

In Ayurvedic medicine, there are 26 different remedies containing *Andrographis paniculata* used to treat liver disorders. Administration of *Andrographis paniculata* prevented hexachlorocyclohexane induced increase in the activities of γ -glutamyl transpeptidase, glutathione-S-transferase and lipid peroxidation in mouse liver, an indication of potential antioxidant and hepatoprotective effects of *Andrographis paniculata*.^{21,22)} Leaf extract of *Andrographis paniculata* and andrographolide were found to be effective in preventing carbontetrachloride-induced liver damage in rats and mice.^{17,25,27)}

Andrographolide also showed significant hepatoprotective effect against various types of liver damage induced by galactosamine^{18,23,24)} or paracetamol,^{17,28)} and had a higher capability than a classical antioxidant silymarin in preventing a decrease of bile production induced by paracetamol.¹⁸⁾ Andrographolide played a hepatoprotective role by reducing a lipid peroxidation product malondialdehyde (MDA), in which the lowering of MDA formation conveyed the free radical scavenging property of diterpene lactones of andrographolide, as well as by maintaining high level of glutathione, glutamic-pyruvate transaminase, and alkaline phosphatase in carbontetrachloride or *tert*-butylhydroperoxide treated mice.¹⁹⁾ Antihepatotoxic action of andrographolide against *Plasmodium berghei* K173-induced hepatic damage of *Mastomys natalensis* was noted.²⁰⁾ In other studies, andrographolide was sug-

gested to play a role as a potent stimulator of gallbladder function by producing a significant increase in bile flow, bile salts, and bile acid in conscious rats and anaesthetized guinea pigs.²⁹⁾ There was marked improvement, *i.e.*, improvement of appetite and liver function tests, gradual recovery from jaundice, subsidence of fever, in the majority of infective hepatitis patients after continuous treatment with *Andrographis paniculata*.²⁹⁾

Immunological Potential

Recent research has excitingly indicated that extracts of *Andrographis paniculata* may have the potential for interfering with the viability of the human immuno-deficiency virus (HIV) and advised that *Andrographis paniculata* could combine with modern medicines against acquired immuno-deficiency syndromes (AIDS).⁵⁹⁾ *Andrographis paniculata* contains substances, one of which is andrographolide, which interrupted or modified the cellular signal transduction pathway of the virus, resulting in interfering the key enzymes and viral reproduction consequently.^{59,60)} It was proposed as a potent stimulator of immune system by two approaches. The first was an antigen-specific response; antibodies were made to counteract invading microbes and the second was a nonspecific immune response; macrophage cells scavenged and destroyed invaders. Since *Andrographis paniculata* activated both responses, it may be effective against a variety of infectious and oncogenic agents.

Andrographolide exhibited prohormone/proprotein convertase (PC) enzyme inhibition against furin, though the activity was relatively weak, compared to that of its succinoylated derivatives. The findings suggested a specific structural modification of the andrographolide skeleton by virtue of the protease inhibitory property, possibly acted by suppressing the proteolytic cleavage of envelope glycoprotein gp160 of HIV, which is known to be PC-mediated, particularly by furin.⁴³⁾ Furthermore, andrographolide has been reported to possess an inhibitory effect on HIV replication and interference with HIV-induced cell fusion.⁴⁰⁻⁴²⁾ Andrographolide promoted interferon (IFN)- α , IFN- γ , tumor necrosis factor (TNF)- α inductions of peripheral blood mononuclear cells (PBMCs), enhanced phagocytosis activity of peritoneal macrophage from guinea pig to phagocytosis cock erythrocyte, as well as augmented the cytotoxicity mediated by natural killer cells from PBMCs to damage the K562 cell lines. These observations

suggested andrographolide as an immunostimulant agent which could modulate both antigen specific and nonspecific immune function by means of its natural killer cells and macrophage and cytokines induction.⁶¹⁾ Besides anti-HIV activity, andrographolide showed viricidal activity against herpes simplex virus 1.¹⁴⁾

A phase I dose-escalating clinical trial conducted in 13 HIV positive patients showed a significant rise in the mean CD4(+) lymphocyte level but with no statistically significant changes in mean plasma HIV-1 RNA levels of HIV-1 infected subjects after administration of the regimen (andrographolide at a dose of 5 mg/kg for 3 weeks, escalating to that of 10 mg/kg for 3 weeks and to that of 20 mg/kg for a final 3 weeks). The findings noted that andrographolide may inhibit HIV-induced cell cycle dysregulation, leading to a rise in CD4(+) lymphocyte levels in HIV-1 infected individuals.⁴⁰⁾

Andrographolide treatment inhibited the *in vitro* proliferation of different human cancer and immune cell lines by exerting direct anticancer activity at the G0/G1 phase of cell cycle arrest through induction of inhibitory protein p27 and decreased expression of cyclin-dependent kinase 4 (CDK4). Immunostimulatory activity of andrographolide was evidenced by increased proliferation of lymphocytes and production of interleukin-2 (IL-2).³³⁾ Likewise, *Andrographis paniculata* extract and andrographolide was found to significantly inhibit growth of human acute myeloid leukemic cells by inducing cell cycle arrest and affecting an intrinsic mitochondria-dependent pathway of apoptosis by regulating expression of some pro-apoptotic markers, namely causing chromosomal DNA fragmentations, an occurrence of apoptosis, induction of Bcl-2-associated X protein (Bax) expression, and decrease of B-cell lymphoma 2 (Bcl-2) proteins in the inhibited cells.³⁴⁾ Moreover, induction of cell cycle arrest at G2/M phase and a late apoptosis of the cells with the collapse of mitochondrial membrane potential and an intracellular increase of hydrogen peroxide but a decrease of superoxide radicals and reduction of glutathione have been reported as well.³⁵⁾ The cytotoxic effect of andrographolide on HepG2 cells was suggested to be the primary attribute to the induction of cell cycle arrest via the alteration of cellular redox status.³⁵⁾ In addition, andrographolide activated apoptosis in human cancer cell lines via activation of caspase-3 and caspase-8 with the participation of mitochondria has been noted.^{36,37,62)} Recently, andrographolide was

reported to possess cytotoxicity to a human oral epidermoid carcinoma cell line.⁶³⁾

Andrographolide also enhanced production of TNF- α and CD marker expression, resulting in increase of cytotoxic activity of lymphocytes against cancer cells, which may contribute for its indirect anticancer activity. Andrographolide also showed *in vivo* anticancer activity against B16F0 melanoma syngenic and HT-29 xenograft models.^{33,60)} In another study, an extract of *Andrographis paniculata* significantly inhibited the proliferation of HT-29 colon cancer cells and augmented the proliferation of human peripheral blood lymphocytes (HPBLs).³²⁾

An ethanolic extract of *Andrographis paniculata* and andrographolide showed promising immunostimulant activity.³⁸⁾ Andrographolide reciprocally showed anticancer and immunostimulatory activities on diverse cancer cells representing different types of human cancers by enhanced proliferation and IL-2 induction in HPBLs.³²⁾ Furthermore, andrographolide demonstrated potent cell differentiation-inducing activity toward mouse myeloid leukemia cells³⁹⁾ and significantly enhanced natural killer cell activity in normal and tumor-bearing animals; antibody-dependent cellular cytotoxicity, mitogen-induced proliferation of splenocyte, thymocyte, and bone marrow cells were increased with significant elevation of production of IL-2 and interferon- γ in normal and Ehrlich ascites carcinoma-bearing animals.⁶⁴⁾

Besides causing cancer cell maturity or differentiation, andrographolide showed selective cytotoxicity to prostate cancer PC-3 cells by inducing cell death through activation of an extrinsic caspase cascade of the apoptotic pathway comparable to that of the widely used and highly toxic drug, cisplatin.⁶⁵⁾ Further, andrographolide was able to efficiently block T cell activation by completely abolishing and interfering with the maturation of dendritic cells, as well as by drastically diminishing antibody response to a thymus-dependent antigen and delayed type hypersensitivity in mice, a feature that could be useful for interfering with detrimental T cell responses.⁴⁴⁾

Anti-inflammatory Activity

Andrographis paniculata is also used as a folk medicinal remedy for fever, pain reduction, and disorders of the intestinal tract. The ability of *Andrographis paniculata* to lower fever has been demonstrated independently in several re-

ports. It has shown that andrographolide lowered the fever produced by different fever-inducing agents, such as bacterial endotoxins, pneumococcus, hemolytic streptococcus, typhoid, paratyphoid, and 2,4-dinitrophenol.⁴⁾ The analgesic activity of andrographolide was weaker than aspirin while anti-pyretic activity was comparable to that of aspirin.^{66,67)}

Andrographolide attenuated the TNF- α -induced intercellular adhesion molecule-1 (ICAM-1) expression and also inhibited the TNF-induced endothelial-monocyte adhesion; those were key steps in the development of inflammation.⁶⁸⁾ An anti-inflammatory benefit of andrographolide by reduction of inducible nitric oxide synthase (iNOS) protein expression through prevention of the *de novo* protein synthesis and decreasing the protein stability via a post-transcriptional mechanism has been inferred.⁷⁻⁹⁾ Furthermore, andrographolide exerted anti-inflammatory effects by inhibiting nuclear factor (NF)- κ B binding to DNA, and thus reducing the expression of pro-inflammatory proteins, such as cyclooxygenase-2 (COX-2).⁶⁹⁾ Another study showed weak anti-inflammatory effects of andrographolide compared to other diterpenoid constituents in the plant,⁴⁾ in which the anti-inflammatory effect probably worked by a mechanism that involves secreted material from adrenal glands, since such effects disappeared in adrenalectomized animals.⁴⁾ The anti-inflammatory effect of andrographolide has also been explained by its ability to inhibit neutrophil adhesion/transmigration through suppression of macrophage adhesion molecule-1 (Mac-1) upregulation which could be mediated by down regulation of reactive oxygen species (ROS) production via a protein kinase C (PKC)-dependent mechanism.^{10,11)} The potent immunosuppressant effects in murine T-cells by significant reduction of IFN- γ production and extracellular-signal-regulated protein kinase (ERK1/2) phosphorylation induced by concanavaline A has been mentioned.⁶²⁾ The ability of andrographolide to inhibit T cell activation was applied to interfere with the onset of Experimental Autoimmune Encephalomyelitis (EAE), an inflammatory demyelinating disease of the central nervous system that is primarily mediated by CD4(+) T cells and serves as an animal model for human multiple sclerosis. Treatment with andrographolide was able to significantly reduce EAE symptoms in mice by inhibiting T cell and antibody responses directed to myelin antigens.⁴⁴⁾

In addition, andrographolide significantly inhibited carrageenin-, kaolin- and nystatin-induced paw oedema. Moreover, it significantly inhibited the weight of granuloma induced by cotton pellet and decreased oedema in adjuvant-induced arthritis, and also inhibited dye leakage in acetic acid-induced vascular permeability. It was devoid of ulcerogenic effect on the stomach of rats.⁷⁰⁾ Presently, a novel formulation comprising of andrographolide, a diterpene lactone, and diterpene triepoxide lactones for synergistic inhibition of COX-2 has been achieved.⁷¹⁾

Inflammation plays an important role in the pathogenesis of several neurodegenerative diseases including Parkinson's disease. Andrographolide has been reported to possess an anti-inflammatory effect *in vitro* by modulating macrophage and neutrophil activity.^{7,8,10,11)} Treatment with andrographolide exhibited a significant protective effect against lipopolysaccharide-induced neurotoxicity in mixed neuron-glia cultures. These findings demonstrate that andrographolide reduced inflammation-mediated dopaminergic neurodegeneration in mesencephalic neuron-glia cultures by inhibiting microglial activation, thus indicating that andrographolide may have clinical utility for the treatment of inflammation-related neurodegenerative disorders such as Parkinson's disease.⁷²⁾

Respiratory System Benefits

Andrographis paniculata has been reviewed to be superior to placebo in alleviating the subjective symptoms of uncomplicated upper respiratory tract infection (URI) and being preliminary evidence of a prevalence effect.⁷³⁾ There was reasonably strong evidence from clinical trials to suggest that *Andrographis paniculata* was effective in reducing the severity and the duration of URI when treatment was started within the first 36–48 hr of symptoms.⁷⁴⁾

Prevention of common cold with *Andrographis paniculata* was studied in a pilot double-blind study. There was a significant decrease in prevalence and intensity of the symptoms in the uncomplicated common colds, compared to the placebo after the *Andrographis paniculata* regimen intake.^{5,75)} The relative risk of catching a cold indicated that the preventive effect could be due to immunostimulatory effects of andrographolide. Moreover, *Andrographis paniculata* accelerated recuperation of common cold patients with symptoms including nasal discharge, nasal stuffiness, sore throat, earache, cough, fever, headache, and malaise.^{5,75,76)}

The mechanism of action of *Andrographis paniculata* in treatment of URI remains unclear to date. The apparent effectiveness of the plant may be based either on its anti-inflammatory properties or on its immunomodulatory properties. Further research is needed both to clarify whether *Andrographis paniculata* is as effective in treatment of URI and to clarify the mechanism through which this benefit is mediated.

Antimalarial Activity

Malaria is still a prevalent disease in many tropical and subtropical countries. *Andrographis paniculata* was found to considerably inhibit the multiplication of *Plasmodium berghei*.¹⁵⁾ The protective action of *Andrographis paniculata* is proposed to be due to reactivation of the key antioxidant enzyme superoxide dismutase.²⁰⁾ In dog, *Andrographis paniculata* extracts effectively killed filaria that obstructed lymph channels, consequently leading to elephantiasis. Another study also reported antimalarial effect of *Andrographis paniculata* against *Plasmodium falciparum*.¹⁶⁾

Antidiarrhoeal and Intestinal Effects

Diarrhea is one of the top ten causes of death worldwide and is a leading cause of death in children in developing countries; especially under five years of age. Many modern drugs used to relieve the symptoms, *i.e.*, kaolin-pectin, bismuth, loperamide, have undesirable side effects. It had been believed that *Andrographis paniculata* was effective against bacterial dysentery and diarrhea, but how it was accomplished has been unclear up to date. Extracts of *Andrographis paniculata* have been shown significant antidiarrhoeal activity against *Escherichia coli* associated diarrhea,^{12,13)} while andrographolide exhibited similar activity to loperamide the most common antidiarrheal drug. In a double blind study, patients with acute diarrhea and bacillary dysentery responded favorably to *Andrographis paniculata*.⁷⁷⁾

Cardiovascular Activity

The effects of *Andrographis paniculata* in an atherosclerotic rabbit model showed increases of the nitric oxide, cyclic guanosine monophosphate, and activity of superoxide dismutase with declines of lipid peroxide and endothelin. These observations suggested the potential of *Andrographis paniculata* as an antioxidant to preserve endothelial function, resulting in maintenance of the balance of nitric oxide/endothelin.⁷⁸⁾ In another study, *Andrographis*

paniculata demonstrated an increase of blood clotting time, thus pre- and post-treatment with the extracts of *Andrographis paniculata* before angioplasty and after surgery significantly prevented constriction of blood vessels, resulting in decreasing risk of subsequent closing of blood vessels (restenosis) after angioplasty procedures.⁷⁸⁾ The arterial narrowing caused by injury to the inner lining of the blood vessel and by high cholesterol in the diet was also found to be decreased by *Andrographis paniculata*.⁷⁹⁾

Besides the benefits on the surgery, it was reported that *Andrographis paniculata* given to dogs one hour after development of myocardial infarction decreased the damage of the heart muscle⁸⁰⁾ and activated fibrinolysis.⁸¹⁾ *Andrographis paniculata* additionally showed antihypertensive effects by relaxing the smooth muscle wall of the blood vessels, consequently resulting in lowering of blood pressure in noradrenaline-treated rats.⁸¹⁾ These observations hinted at the potential of *Andrographis paniculata* as a good option for cardiovascular therapy.

The cardiovascular activities of a crude extract of *Andrographis paniculata* and andrographolide were elucidated in anaesthetized rats. The hypotensive effects of the *Andrographis paniculata* extract occurred in the absence of significant change in heart rate, indicating more contribution of the hypotensive response on cardiovascular activity than a direct action on the heart, and was finally proposed to be mediated through α -adrenoceptors, autonomic ganglion and histaminergic receptors.^{30,31)} However, it was considered that andrographolide was not the hypotensive active compound of *Andrographis paniculata*.

Psycho-pharmacological Activity

Psycho-pharmacological studies were conducted with an extract of *Andrographis paniculata*. It was evident that the extract had a potent central nervous system (CNS) depressant action as indicated by its hypnotic potentiation effect; it produced hypothermia and exhibited an analgesic action against acetic acid-induced writhing, by the same mechanism as reserpine and chlorpromazine.⁸²⁾ Moreover, reduction in exploratory behaviors with the extract was in conformity with similar actions produced by other CNS depressant drugs.⁸³⁾ The extract also exhibited significant motor incoordination and muscle relaxant activity. These findings revealed a potent CNS-depressant action of *Andrographis paniculata*, though it could not predict

its CNS category at present.⁸²⁾ The extract also produced a prolongation of the pentobarbitone-induced sleeping time and lowered the body temperature in different experimental animal models.⁸²⁾

Hypoglycemic Activity

A water extract of *Andrographis paniculata* significantly prevented induction of hyperglycemia induced by oral administration of glucose in rabbits, but it failed to do so in adrenaline-induced hyperglycemia. Additionally, long-term administration (6 weeks) of *Andrographis paniculata* was incapable to demonstrate fasting blood sugar lowering effect. Hence, *Andrographis paniculata* might prevent glucose absorption from gut.⁸⁴⁾

Anti-fertility Activity

Andrographis paniculata possessed anti-fertility and pregnancy-terminating effects⁸⁵⁾ and stopped spermatogenesis in male rats.⁸⁶⁾ None of the female mice that daily consumed *Andrographis paniculata* mixed food became pregnant when mated with the male of potential fertility who did not receive the treatment.⁸⁷⁾ The observations suggested an antispermatogenic or antiandrogenic abilities as well as ovulation preventive effect of the plant. Hence, using of the herb during pregnancy should be avoided.

Andrographis paniculata and andrographolide proved to affect spermatogenesis in rats by preventing cytokinesis of the dividing spermatogenic cell lines with appearances of sertoli cell damage and a spermatotoxic effect.^{45,88)} The study pointed to a male reproductive toxic effect of a therapeutic use of andrographolide and confirmed the possible prospective use of andrographolide as a male contraceptive.⁴⁵⁾ Changes in the biochemical parameters in rats, such as significant decreases in protein content, but marked increases in cholesterol, acid phosphatase, and alkaline phosphatase levels with appearance of fructose in the reproductive system, suggested anti-fertility effects of the andrographolide.⁸⁹⁾

ANDROGRAPHIS PANICULATA AND CYTOCHROME P450S

An extract of *Andrographis paniculata* including andrographolide and its analogues have been reported to exhibit a marked effect on hep-

atic metabolizing enzymes, *i.e.*, aniline hydroxylase, *N*- and *O*-demethylase (Choudhury and Poddar, 1984), alanine aminotransferase and aspartate aminotransferase,²¹⁾ including phase II enzymes, *i.e.*, glutathione *S*-transferase and DT-diaphorase.⁹⁰⁾ Modulatory influence of *Andrographis paniculata* on a responsive isoform of hepatic cytochrome P450s (P450) was reported in mouse livers compared to typical inducers (3-methylcholanthrene (3-MC) for CYP1A and phenobarbital (PB) for CYP2B).⁹¹⁾ In mice administered with an extract of *Andrographis paniculata* or 3-MC, the P450 content was comparable to the untreated mice, whereas for those PB treated; the P450 content was markedly increased. 3-MC significantly increased ethoxyresorufin *O*-deethylase (EROD) and methoxyresorufin *O*-demethylase activities, whereas pentoxyresorufin *O*-deethylase (PROD) activity was markedly elevated by PB. These results conveyed CYP1A1 and CYP2B10 as responsive P450 isoforms for *Andrographis paniculata*.⁹¹⁾

Andrographolide significantly induced the expression level of CYP1A1 mRNA, protein, and enzyme in a concentration-dependent manner in monolayer-cultured hepatocytes. Co-treatment with andrographolide and a typical inducer benz[*a*]anthracene (B[*a*]A) synergistically enhanced the expression level of CYP1A1 mRNA, in which the expression was blocked by resveratrol, an arylhydrocarbon receptor (AhR) antagonist.⁹²⁾ These observations hint that an AhR-mediated transcription activation pathway possibly participates in the synergistic effect of concomitant treatment with andrographolide and B[*a*]A on CYP1A1 mRNA expression. Therefore, andrographolide might influence the expression mechanism of *CYP1A1* by enhanced efficiency of mRNA processing or inhibition of mRNA turnover. In addition, a robust increased expression of UGT1A6 mRNA which belongs to a battery of AhR-mediated genes by andrographolide was noted (our unpublished observations). Andrographolide extensively induced CYP1A1 expression, while it induced CYP1A2 less markedly, and did not induce CYP1B1 expression.⁹²⁾ These observations could be explained by the different mechanisms of transcriptional regulation among CYP1A1, CYP1A2, and CYP1B1.^{93,94)}

Safety and Contraindications

In Traditional Chinese Medicine (TCM) and in systems of traditional medicine of Thailand and In-

dia, *Andrographis paniculata* has long been perceived as safe. No subchronic testicular toxicity was found in male rats treated with the standardized dried extract of *Andrographis paniculata* as evaluated by reproductive organ weight, testicular histology, ultrastructural analysis of Leydig cells and testosterone levels after a period of 60 days-treatment.⁹⁵⁾ Anaphylactic shock (one case) and anaphylactic reactions (two cases) have been reported to the World Health Organization (WHO) Collaborating Center for International Drug Monitoring as of June 2003.⁷³⁾ Adverse effects reported in trials to date are mild, infrequent, and self-limiting, including allergic reaction, fatigue, headache, lymph node pain, lymphadenopathy, nausea, diarrhea, and metallic taste.⁷⁴⁾ Most trials to date are of short duration (two weeks or less in general), then prediction on the safety of longer term use is implausible. Therefore, using of *Andrographis paniculata* as an alternative medicinal therapy or for health promotion during physical condition out of the ordinary should be cautious.

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REFERENCES

- 1) Tapsell, L. C., Hemphill, I., Cobiac, L., Patch, C. S., Sullivan, D. R., Fenech, M., Roodenrys, S., Keogh, J. B., Clifton, P. M., Williams, P. G., Fazio, V. A. and Inge, K. E. (2006) Health benefits of herbs and spices: The past, the present, the future. *Med. J. Aust.*, **21**, S4–S24.
- 2) Zhang, X. (2004) *WHO monograph on selected medicinal plants*, vol. 2, World Health Organization, Geneva.
- 3) Mishra, S. K., Sangwan, N. S. and Sangwan, R. S. (2007) *Andrographis paniculata* (Kalmegh): A review. *Pharmacog. Rev.*, **1**, 283–298.
- 4) Deng, W. L. (1978) Preliminary studies on the pharmacology of the *Andrographis* product dihydroandrographolide sodium succinate. *Newsletter Chinese Herbal Medicine*, **8**, 26–28.
- 5) Caceres, D. D., Hancke, J. L., Burgos, R. A. and Wikman, G. K. (1997) Prevention of common colds with *Andrographis paniculata* dried extract: A pilot double-blind trial. *Phytomedicine*, **4**, 101–104.
- 6) Pholphana, N., Rangkadilok, N., Thongnest, S., Ruchirawat, S., Ruchirawat, M. and Satayavivad, J.

- (2004) Determination and variation of three active diterpenoids in *Andrographis paniculata* (Burm.f.) Nees. *Phytochem. Anal.*, **15**, 365–371.
- 7) Chiou, W. F., Chen, C. F. and Lin, J. J. (1998) Andrographolide suppresses the expression of inducible nitric oxide synthase in macrophage and restores the vasoconstriction in rat aorta treated with lipopolysaccharide. *Br. J. Pharmacol.*, **125**, 327–334.
 - 8) Chiou, W. F., Chen, C. F. and Lin, J. J. (2000) Mechanisms of suppression of inducible nitric oxide synthase (iNOS) expression in RAW 264.7 cells by andrographolide. *Br. J. Pharmacol.*, **129**, 1553–1560.
 - 9) Sheeja, K., Shihab, P. K. and Kuttan, G. (2006) Antioxidant and anti-inflammatory activities of the plant *Andrographis Paniculata* Nees. *Immunopharmacol. Immunotoxicol.*, **28**, 129–140.
 - 10) Shen, Y. C., Chen, C. F. and Chiou, W. F. (2000) Suppression of rat neutrophil reactive oxygen species production and adhesion by the diterpenoid lactone andrographolide. *Planta Med.*, **66**, 314–317.
 - 11) Shen, Y. C., Chen, C. F. and Chiou, W. F. (2002) Andrographolide prevents oxygen radical production by human neutrophils: possible mechanism(s) involved in its anti-inflammatory effect. *Br. J. Pharmacol.*, **135**, 399–406.
 - 12) Gupta, S., Choudhry, M. A., Yadava, J. N. S., Srivastava, V. and Tandon, J. S. (1990) Antidiarrhoeal activity of diterpenes of *Andrographis paniculata* (Kal-Megh) against *Escherichia coli* enterotoxin in *in vivo* models. *Int. J. Crude Drug Res.*, **28**, 273–283.
 - 13) Gupta, S., Yadava, J. N. S. and Tandon, J. S. (1993) Antisecretory (antidiarrhoeal) activity of Indian medicinal plants against *Escherichia Coli* enterotoxin-induced secretion in rabbit and guinea pig ileal loop models. *Pharm. Biol.*, **31**, 198–204.
 - 14) Wiart, C., Kumar, K., Yusof, M. Y., Hamimah, H., Fauzi, Z. M. and Sulaiman, M. (2005) Antiviral properties of ent-labdene diterpenes of *Andrographis paniculata* Nees, inhibitors of herpes simplex virus type 1. *Phytother. Res.*, **19**, 1069–1070.
 - 15) Misra, P., Pal, N. L., Guru, P. Y., Katiyar, J. C., Srivastava, V. and Tandon, J. S. (1992) Antimalarial activity of *Andrographis paniculata* (Kalmegh) against *Plasmodium berghei* NK 65 in *Mastomys natalensis*. *International Journal of Pharmacognosy*, **30**, 263–274.
 - 16) Rahman, N. N. N. A., Furuta, T., Kojima, S., Takane, K. and Mohd, M. A. (1999) Antimalarial activity of extracts of Malaysian medicinal plants. *J. Ethnopharmacol.*, **64**, 249–254.
 - 17) Handa, S. S. and Sharma, A. (1990) Hepatoprotective activity of andrographolide from *Andrographis paniculata* against carbontetrachloride. *Indian J. Med. Res.*, **92**, 276–283.
 - 18) Handa, S. S. and Sharma, A. (1990) Hepatoprotective activity of andrographolide against galactosamine & paracetamol intoxication in rats. *Indian J. Med. Res.*, **92**, 284–292.
 - 19) Kapil, A., Koul, I. B., Banerjee, S. K. and Gupta, B. D. (1993) Antihepatotoxic effects of major diterpenoid constituents of *Andrographis paniculata*. *Biochem. Pharmacol.*, **46**, 182–185.
 - 20) Chander, R., Srivastava, V., Tandon, J. S. and Kapoor, N. K. (1995) Antihepatotoxic activity of diterpenes of *Andrographis Paniculata* (Kal-Megh) against *Plasmodium Berghei-Induced* hepatic damage in *Mastomys Natalensis*. *Pharm. Biol.*, **33**, 135–138.
 - 21) Trivedi, N. and Rawal, U. M. (2000) Hepatoprotective and toxicological evaluation of *Andrographis paniculata* on severe liver damage. *Indian J. Pharmacol.*, **32**, 288–293.
 - 22) Trivedi, N. and Rawal, U. M. (2001) Hepatoprotective and antioxidant property of *Andrographis paniculata* (Nees) in BHC induced liver damage in mice. *Indian J. Exp. Biol.*, **39**, 41–46.
 - 23) Visen, P. K. S., Saraswat, B., Vuksan, V. and Dhawan, B. N. (2007) Effect of andrographolide on monkey hepatocytes against galactosamine induced cell toxicity: An *in-vitro* study. *Journal Complementary and Integrative Medicine*, **4**, 10.
 - 24) Sarawat, B., Visen, P. K. S., Patnaik, G. K. and Dhawan, B. N. (1995) Effect of andrographolide against galactosamine-induced hepatotoxicity. *Fitoterapia*, **66**, 415–420.
 - 25) Choudhury, B. R. and Poddar, M. K. (1984) Andrographolide and kalmegh (*Andrographis paniculata*) extract: *in vivo* and *in vitro* effect on hepatic lipid peroxidation. *Methods Find. Exp. Clin. Pharmacol.*, **6**, 481–485.
 - 26) Choudhury, B. R., Haque, S. J. and Poddar, M. K. (1987) *In vivo* and *in vitro* effects of Kalmegh (*Andrographis paniculata*) extract and andrographolide on hepatic microsomal enzymes. *Planta Med.*, **53**, 135–140.
 - 27) Rana, A. C. and Avadhoot, Y. (1991) Hepatoprotective effects of *Andrographis paniculata* against carbon tetrachloride-induced liver damage. *Arch. Pharm. Res.*, **14**, 93–95.
 - 28) Visen, P. K., Shukla, B., Patnaik, G. K. and Dhawan, B. N. (1993) Andrographolide protects rat hepatocytes against paracetamol-induced damage. *J. Ethnopharmacol.*, **40**, 131–136.

- 29) Shukla, B., Visen, P. K. S., Patnaik, G. K. and Dhawan, B. N. (1992) Choleric effect of andrographolide in rats and guinea pigs. *Planta Med.*, **58**, 146–148.
- 30) Zhang, C. Y. and Tan, B. K. H. (1997) Mechanisms of cardiovascular activity of *Andrographis paniculata* in the anaesthetized rat. *J. Ethnopharmacol.*, **56**, 97–101.
- 31) Tan, B. K. H. and Zhang, C. Y. (2004) *Andrographis paniculata* and the cardiovascular system. In *Herbal and Traditional Medicine: Molecular Aspects on Health* (Packer, L., Ong, C. N. and Halliwell, B., Eds.). CRC Press, Taipei, pp. 441–456.
- 32) Kumar, R. A., Sridevi, K., Kumar, N. V., Nanduri, S. and Rajagopal, S. (2004) Anticancer and immunostimulatory compounds from *Andrographis paniculata*. *J. Ethnopharmacol.*, **92**, 291–295.
- 33) Rajagopal, S., Kumar, R. A., Deevi, D. S., Satyanarayana, C. and Rajagopalan, R. (2003) Andrographolide, a potential cancer therapeutic agent isolated from *Andrographis paniculata*. *J. Exp. Ther. Oncol.*, **3**, 147–158.
- 34) Cheung, H. Y., Cheung, S. H., Li, J., Cheung, C. S., Lai, W. P., Fong, W. F. and Leung, F. M. (2005) Andrographolide isolated from *Andrographis paniculata* induces cell cycle arrest and mitochondrial-mediated apoptosis in human leukemic HL-60 cells. *Planta Med.*, **71**, 1106–1111.
- 35) Li, J., Cheung, H. Y., Zhang, Z., Chan, G. K. L. and Fong, W. F. (2007) Andrographolide induces cell cycle arrest at G2/M phase and cell death in HepG2 cells via alteration of reactive oxygen species. *Eur. J. Pharmacol.*, **568**, 31–44.
- 36) Sukardiman, H., Widyawaruyanti, A., Sismindari and Zaini, N. C. (2007) Apoptosis inducing effect of andrographolide on TD-47 human breast cancer cell line. *African Journal of Traditional Complementary and Alternative Medicines*, **4**, 345–351.
- 37) Zhou, J., Zhang, S., Ong, C. and Shen, H. (2006) Critical role of pro-apoptotic Bcl-2 family members in andrographolide-induced apoptosis in human cancer cells. *Biochem. Pharmacol.*, **72**, 132–144.
- 38) Puri, A., Saxena, R., Saxena, R. P. and Saxena, K. C. (1993) Immunostimulant agents from *Andrographis paniculata*. *J. Nat. Prod.*, **56**, 995–999.
- 39) Matsuda, T., Kuroyanagi, M., Sugiyama, S., Umehara, K., Ueno, A. and Nishi, K. (1994) Cell differentiation-inducing diterpenes from *Andrographis paniculata* Nees. *Chem. Pharm. Bull. (Tokyo)*, **42**, 1216–1225.
- 40) Calabrese, C., Berman, S. H., Babish, J. G., Ma, X., Shinto, L., Dorr, M., Wells, K., Wenner, C. A. and Standish, L. J. (2000) A phase I trial of andrographolide in HIV positive patients and normal volunteers. *Phytother. Res.*, **14**, 333–338.
- 41) Otake, T., Mori, H., Morimoto, M., Ueba, N., Sutardjo, S., Kusumoto, I. T., Hattori, M. and Namba, T. (1995) Screening of Indonesian plant extracts for anti-human immunodeficiency virus-type 1 (HIV-1) activity. *Phytother. Res.*, **9**, 6–10.
- 42) Chang, R. S., Ding, L., Chen, G. Q., Pan, Q. C., Zhao, Z. L. and Smith, K. M. (1991) Dehydroandrographolide succinic acid monoester as an inhibitor against the human immunodeficiency virus. *Proc. Soc. Exp. Biol. Med.*, **197**, 59–66.
- 43) Basak, A., Cooper, S., Roberge, A. G., Banik, U. K., Chrétien, M. and Seidah, N. G. (1999) Inhibition of proprotein convertases-1, -7, and furin by diterpenes of *Andrographis paniculata* and their succinoyl esters. *Biochem. J.*, **338**, 107–113.
- 44) Iruretagoyena, M. I., Tobar, J. A., Gonzalez, P. A., Sepulveda, S. E., Figueroa, C. A., Burgos, R. A., Hancke, J. L. and Kalergis, A. M. (2005) Andrographolide interferes with T cell activation and reduces experimental autoimmune encephalomyelitis in the mouse. *J. Pharmacol. Exp. Ther.*, **312**, 366–372.
- 45) Akbarsha, M. A. and Murugaian, P. (2000) Aspects of the male reproductive toxicity/male antifertility property of andrographolide in albino rats: Effect on the testis and the cauda epididymidal spermatozoa. *Phytother. Res.*, **14**, 432–435.
- 46) Nanduri, S., Nyavanandi, V. K., Thunuguntla, S. S., Kasu, S., Pallerla, M. K., Ram, P. S., Rajagopal, S., Kumar, R. A., Ramanujam, R., Babu, J. M., Vyas, K., Devi, A. S., Reddy, G. O. and Akella, V. (2004) Synthesis and structure-activity relationships of andrographolide analogues as novel cytotoxic agents. *Bioorg. Med. Chem. Lett.*, **18**, 4711–4717.
- 47) Sandberg, F. (1994) *Andrographidis herba Chuanxinlian: A review*. Swedish Herbal Institute, Gothenburg, Sweden.
- 48) Pramanick, S., Banerjee, S., Achari, B., Das, B., Sen, A. K., Mukhopadhyay, S., Neuman, A. and Prangé, T. (2006) Andropanolide and isoandrographolide, minor diterpenoids from *Andrographis paniculata*: Structure and X-ray crystallographic analysis. *J. Nat. Prod.*, **69**, 403–405.
- 49) Chen, W. and Liang, X. (1982) Deoxyandrographolide 19 β -D-glucoside from the leaves of *A. paniculata*. *Planta Med.*, **15**, 245–246.
- 50) Sharma, A., Krishan, L. and Handa, S. S. (1992) Standardization of the Indian crude drug Kalmegh by high pressure liquid chromatographic determination of andrographolide. *Phytochem. Anal.*, **3**, 129–131.

- 51) Siripong, P., Kongkathip, B., Preechanukool, K., Picha, P., Tunsuwan, K. and Taylor, W. C. (1992) Cytotoxic diterpenoid constituents from *Andrographis paniculata* Nees leaves. *J. Sci. Soc. Thailand*, **18**, 187–194.
- 52) Cui, L., Qiu, F., Wang, N. and Yao, X. (2004) Four new andrographolide metabolites in human urine. *Chem. Pharm. Bull. (Tokyo)*, **52**, 772–775.
- 53) Panossian, A., Hovhannisyann, A., Mamikonyan, G., Abrahamian, H., Hambardzumyan, E., Gabrielian, E., Goukasova, G., Wikman, G. and Wagner, H. (2000) Pharmacokinetics and oral bioavailability of andrographolide from *Andrographis paniculata* fixed combination Kan Jang in rats and human. *Phytomedicine*, **7**, 351–364.
- 54) He, X., Li, J. K., Gao, H., Qiu, F., Hu, K., Cui, X. M. and Yao, X. S. (2003) Four new andrographolide metabolites in rats. *Tetrahedron*, **59**, 6603–6607.
- 55) He, X., Li, J. K., Gao, H., Qiu, F., Hu, K., Cui, X. M. and Yao, X. S. (2003) Six new andrographolide metabolites in rats. *Chem. Pharm. Bull. (Tokyo)*, **51**, 586–589.
- 56) He, X., Li, J. K., Gao, H., Qiu, F., Hu, K., Cui, X. M. and Yao, X. S. (2003) Identification of a rare sulfonic acid metabolite of andrographolide in rats. *Drug Metab. Dispos.*, **31**, 983–985.
- 57) Cui, L., Qiu, F. and Yao, X. (2005) Isolation and identification of seven glucuronide conjugates of andrographolide in human urine. *Drug Metab. Dispos.*, **33**, 555–562.
- 58) Meng, Z. M. (1981) Studies on the structure of the adduct of andrographolide with sodium hydrogen sulfite. *Acta Pharmacol. Sin.*, **16**, 571–575.
- 59) Stephen, H. and Comac, L. (2000) *Miracle herbs: How herbs combine with modern medicine to treat cancer, heart disease, AIDS, and more*, Kensington Publishing Corporation, New York.
- 60) Nanduri, S., Rajagopal, S. and Akella, V. (2003) United States Patent 6576662. Compounds having anticancer activity: Process for their preparation and pharmaceutical compositions containing them (US Patent Issued on June 10, 2003).
- 61) Peng, G. Y., Zhou, F., Ding, R. L., Li, H. D. and Yao, K. (2002) Modulation of lianbizi injection (andrographolide) on some immune functions. *Zhongguo Zhong Yao Za Zhi.*, **27**, 147–150 (in Chinese).
- 62) Burgos, R. A., Seguel, K., Perez, M., Meneses, A., Ortega, M., Guard, M. I., Loaiza, A. and Hancke, J. L. (2005) Andrographolide inhibits IFN- γ and IL-2 cytokine production and protects against cell apoptosis. *Planta Med.*, **71**, 429–434.
- 63) Li, W., Xu, X., Zhang, H., Ma, C., Fong, H., Van Breemen, R. and Fitzloff, J. (2007) Secondary metabolites from *Andrographis paniculata*. *Chem. Pharm. Bull. (Tokyo)*, **55**, 455–458.
- 64) Sheeja, K. and Kuttan, G. (2007) Antibody-dependent complement-mediated cytotoxicity by andrographolide in normal and ehrlich ascites carcinoma-bearing mice. *Integr. Cancer Ther.*, **6**, 66–73.
- 65) Kim, T. G., Hwi, K. K. and Hung, C. S. (2005) Morphological and biochemical changes of andrographolide-induced cell death in human prostatic adenocarcinoma PC-3 cells. *In Vivo*, **19**, 551–557.
- 66) Vedavathy, S. and Rao, K. N. (1991) Antipyretic activity of six indigenous medicinal plants of Tirumala Hills, Andhra Pradesh, India. *J. Ethnopharmacol.*, **33**, 193–196.
- 67) Madav, H. C., Tripathi, T. and Mishra, S. K. (1995) Analgesic, antipyretic, and antiulcerogenic effects of andrographolide. *Indian J. Pharm. Sci.*, **57**, 121–125.
- 68) Habtemariam, S. (1998) Andrographolide inhibits the tumour necrosis factor- α -induced upregulation of ICAM-1 expression and endothelial-monocyte adhesion. *Phytother. Res.*, **12**, 37–40.
- 69) Hidalgo, M. A., Romero, A., Figueroa, J., Cortés, P., Concha, I. I., Hancke, J. L. and Burgos, R. A. (2005) Andrographolide interferes with binding of nuclear factor- κ B to DNA in HL-60-derived neutrophilic cells. *Br. J. Pharmacol.*, **144**, 680–686.
- 70) Madav, S., Tandan, S. K., Lal, J. and Tripathi, H. C. (1996) Anti-inflammatory activity of andrographolide. *Fitoterapia*, **67**, 452–458.
- 71) Babish, J. G., Howell, T. and Pacioretty, L. (2003) United States Patent 6629835. Combinations of diterpene triepoxide lactones and diterpene lactones or triterpenes for synergistic inhibition of cyclooxygenase-2 (US Patent Issued on October 7, 2003).
- 72) Wang, T., Liu, B., Zhang, W., Wilson, B. and Hong, J. S. (2004) Andrographolide reduces inflammation-mediated dopaminergic neurodegeneration in mesencephalic neuron-glia cultures by inhibiting microglial activation. *J. Pharmacol. Exp. Ther.*, **308**, 975–983.
- 73) Coon, J. T. (2004) *Andrographis paniculata* in the treatment of upper respiratory tract infection: A systematic review of safety and efficacy. *Planta Med.*, **70**, 293–298.
- 74) Kligler, B., Ulbricht, C., Basch, E., Kirkwood, C. D., Abrams, T. R., Miranda, M., Khalsa, K. P. S., Giles, M., Boon, H. and Woods, J. (2006) *Andrographis paniculata* for the treatment of upper respiratory infection: A systematic review by the natural

- standard research collaboration. *The Journal of Science and Healing*, **2**, 25–29.
- 75) Caceres, D. D., Hancke, J. L., Burgos, R. A., Sandberg, F. and Wikman, G. K. (1999) Use of visual analogue scale measurements (VAS) to assess the effectiveness of standardized *Andrographis paniculata* extract SHA-10 in reducing the symptoms of common cold. A randomized double blind-placebo study. *Phytomedicine*, **6**, 217–223.
- 76) Gabrielian, E. S., Shukarian, A. K., Goukasova, G. I., Chandanian, G. L., Panossian, A. G., Wikman, G. and Wagner, H. (2002) A double blind, placebo-controlled study of *Andrographis paniculata* fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis. *Phytomedicine*, **9**, 589–597.
- 77) Thanagkul, B. and Chaichantipayut, C. (1985) Double-blind study of *Andrographis paniculata* Nees and tetracycline in acute diarrhea and bacillary dysentery. *Ramathibodi Medical Journal*, **8**, 57–61.
- 78) Wang, H. W., Zhao, H. Y. and Xiang, S. Q. (1997) Effects of *Andrographis paniculata* component on nitric oxide, endothelin, and lipid peroxidation in experimental atherosclerotic rabbits. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, **17**, 547–549 (in Chinese).
- 79) Wang, D. and Zhao, H. (1993) Experimental studies on prevention of atherosclerotic arterial stenosis and restenosis after angioplasty with *Andrographis paniculata* Nees and fish oil. *J. Tongji Med. Univ.*, **13**, 193–198.
- 80) Zhao, H. and Fang, W. (1990) Protective effects of *Andrographis paniculata* Nees on post-infarction myocardium in experimental dogs. *J. Tongji Med. Univ.*, **10**, 212–217.
- 81) Huang, L. Y. (1987) The effects of andrographolides on experimental blood deficiency of cardiac muscle. *Chinese Herbal Medicine*, **18**, 26–28.
- 82) Mandal, S. C., Dhara, A. K. and Maiti, B. C. (2001) Studies on psychopharmacological activity of *Andrographis paniculata* extract. *Phytother. Res.*, **15**, 253–256.
- 83) Dorr, M., Jayce, D., Porsolt, R. D., Steinberg, H., Summerfield, A. and Tomkiewicz, M. (1971) Persistence of dose related behaviour in mice. *Nature*, **231**, 121–123.
- 84) Borhanuddin, M., Shamsuzzoha, M. and Hussain, A. H. (1994) Hypoglycaemic effects of *Andrographis paniculata* Nees on non-diabetic rabbits. *Bangladesh Med. Res. Counc. Bull.*, **20**, 24–26.
- 85) Kamal, R., Gupta, R. S. and Lohiya, N. K. (2003) Plants for male fertility regulation. *Phytother. Res.*, **17**, 579–590.
- 86) Akbarsha, M. A., Manivanan, B., Hamid, K. S. and Vijayan, B. (1990) Antifertility effect of *Andrographis paniculata* (Nees) in male albino rat. *Indian J. Exp. Biol.*, **28**, 421–426.
- 87) Zoha, M. S., Hussain, A. H. and Choudhury, S. A. (1989) Antifertility effects of *Andrographis paniculata* in mice. *Bangladesh Med. Res. Counc. Bull.*, **15**, 34–37.
- 88) Akbarsha, M. A. and Manivannan, B. (1993) Biochemical changes in the testis and male accessory organs of albino rats on treatment with *Andrographis paniculata* Nees. *Complementary Animal Physiology*, **28**, 421–426.
- 89) Janarthanan, S. (1990) Antifertility effects of andrographolide in rats. *Journal of Ecobiology*, **2**, 325–329.
- 90) Singh, R. P., Banerjee, S. and Rao, A. R. (2001) Modulatory influence of *Andrographis paniculata* on mouse hepatic and extrahepatic carcinogen metabolizing enzymes and antioxidant status. *Phytother. Res.*, **15**, 382–390.
- 91) Jarukamjorn, K., Don-in, K., Makejaruskul, C., Laha, T., Daodee, S., Pearaksa, P. and Sripanidkulchai, B. (2006) Impact of *Andrographis paniculata* crude extract on mouse hepatic cytochrome P450 enzymes. *J. Ethnopharmacol.*, **105**, 464–467.
- 92) Jaruchotikamol, A., Jarukamjorn, K., Sirisangtrakul, W., Sakuma, T., Kawasaki, Y. and Nemoto, N. (2007) Strong synergistic induction of CYP1A1 expression by andrographolide plus typical CYP1A inducers in mouse hepatocytes. *Toxicol. Appl. Pharmacol.*, **224**, 156–162.
- 93) Guengerich, F. P. and Shimada, T. (1998) Activation of procarcinogens by human cytochrome P450 enzymes. *Mutat. Res.*, **400**, 201–213.
- 94) Iwanari, M., Nakajima, M., Kizu, R., Hayakawa, K. and Yokoi, T. (2002) Induction of CYP1A1, CYP1A2, and CYP1B1 mRNAs by nitropoly-cyclic aromatic hydrocarbons in various human tissue-derived cells: chemical-, cytochrome P450 isoforms-, and cell-specific differences. *Arch. Toxicol.*, **76**, 287–298.
- 95) Burgos, R. A., Caballero, E. E., Sfinchez, N. S., Schroeder, R. A., Wikman, G. K. and Hancke, J. L. (1997) Testicular toxicity assesment of *Andrographis paniculata* dried extract in rats. *J. Ethnopharmacol.*, **58**, 219–224.