Andrographis paniculata: A Review of Pharmacological Activities and Clinical Effects

Shahid Akbar, MD, PhD

Introduction

Andrographis paniculata is a plant that has been effectively used in traditional Asian medicines for centuries. Its perceived "blood purifying" property results in its use in diseases where blood "abnormalities" are considered causes of disease, such as skin eruptions, boils, scabies, and chronic undetermined fevers. The aerial part of the plant, used medicinally, contains a large number of chemical constituents, mainly lactones, diterpenoids, diterpene glycosides, flavonoids, and flavonoid glycosides. Controlled clinical trials report its safe and effective use for reducing symptoms of uncomplicated upper respiratory tract infections. Since many of the disease conditions commonly treated with *A. paniculata* in traditional medical systems are considered self-limiting, its purported benefits need critical evaluation. This review summarizes current scientific findings and suggests further research to verify the therapeutic efficacy of *A. paniculata*.

A. paniculata, known on the Indian subcontinent as Chirayetah and Kalmegh in Urdu and Hindi languages, respectively, is an annual plant, 1-3 ft high, that is one of the most commonly used plants in the traditional systems of Unani and Ayurvedic medicines. It is called Creat in English and is known as the "king of bitters." It grows in hedge rows throughout the plains of India and is also cultivated in gardens.[1,2] It also grows in many other Asian countries and is used as a traditional herbal medicine in China, Hong Kong, the Philippines, Malaysia, Indonesia, and Thailand.

The aerial parts are most commonly used; however, the whole plant or roots are mentioned for certain limited purposes in some manuscripts. Traditionally, the plant was used as an infusion, decoction, or powder, either alone or in combination with other medicinal plants. In modern times, and in many controlled clinical trials, commercial preparations have tended to be standardized extracts of the whole plant.

Since many disease conditions commonly treated with *A. paniculata* in traditional medical systems are considered self-limiting, its purported benefits need critical evaluation. This review summarizes current scientific findings and suggests areas where further research is needed.

Uses in Traditional Medical Systems

A. paniculata has been reported as having antibacterial, antifungal, antiviral, choleretic, hypoglycemic, hypocholesterolemic, and adaptogenic effects.[3] In the Unani system of medicine, it is considered aperient, anti-inflammatory, emollient, astringent, diuretic, emmenagogue, gastric and liver tonic, carminative, antihelmintic, and antipyretic. Due to its "blood purifying" activity it is recommended for use in cases of leprosy, gonorrhea, scabies, boils, skin eruptions, and chronic and seasonal fevers.[1] Juice or an infusion of fresh

Shahid Akbar, MD, PhD – Chairman and professor, department of pharmacology, Qassim University, Saudi Arabia; former professor of pharmacology, Medical University of the Americas, Nevis, West Indies; Editor, International Journal of Health Sciences; author of book *Garlic – The Stinking Magic Herb*
Correspondence Address: College of Pharmacy, Qassim University, P.O. Box 6800, Buraidah 51452, Kingdom of Saudi Arabia
Email: shahidakbar@sbcglobal.net or drakbarmdphd@gmail.com

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leaves is given to infants to relieve griping, irregular bowel habits, and loss of appetite.[2,4,5] The leaves and root are also used in general debility, during convalescence after fevers, for dyspepsia associated with gaseous distension, and in advanced stages of dysentery.[4,5]

In China, the herb derived from the leaves or aerial parts of *A. paniculata* is known as Chuanxinlian, Yijianxi or Lanhelian. It is described as bitter and cold, is considered to be antipyretic, detoxicant, anti-inflammatory, and detumescent, and is thought to remove "pathogenic heat" from the blood. *A. paniculata* is used for the treatment of pharyngolaryngitis, diarrhea, dysentery, cough with thick sputum, carbuncle, sores, and snake bites.[6] Various preparations and compound formulas of the herb have been used to treat infectious and non-infectious diseases, with significant effective rates reported for conditions such as epidemic encephalitis B, suppurative otitis media, neonatal subcutaneous annular ulcer, vaginitis, cervical erosion, pelvic inflammation, herpes zoster, chicken pox, mumps, neurodermatitis, eczema, and burns.[6]

Modern Uses

A primary modern use of *A. paniculata* is for the prevention and treatment of the common cold. It appears to have antithrombotic actions, suggesting a possible benefit in cardiovascular disease.[7] Pharmacological and clinical studies suggest the potential for beneficial effects in diseases like cancer[8-12] and HIV infections.[13]

Phytoconstituents

A. paniculata contains diterpenes, lactones, and flavonoids. Flavonoids mainly exist in the root, but have also been isolated from the leaves. The aerial parts contain alkanes, ketones, and aldehydes. Although it was initially thought that the bitter substance in the leaves was the lactone andrographolide, later investigations showed that the leaves contained two bitter principles – andrographolide and a compound named kalmeghin. Four lactones – chuanxinlian A (deoxyandrographolide), B (andrographolide), C (neoandrographolide) and D (14-deoxy-11, 12-didehydroandrographolide) – were isolated from the aerial parts in China.[6] A diterpene glucoside (deoxyandrographolide-19beta-D-glucoside) has been detected in the leaves[14] and six diterpenoids of the ent-labdane type, two diterpene glucosides and four diterpene dimers (bis-andrographolides A, B, C, and D) have been isolated from aerial parts.[15] Two flavonoids identified as 5,7,2',3'-tetramethoxyflavanone and 5-hydroxy-7,2',3'-trimethoxyflavone were isolated from the whole plant,[16] while 12 new flavonoids and 14 diterpenoids have been reported from the aerial parts.[17,18] Two new flavonoid glycosides and a new diterpenoid (andrographic acid) were recently reported,[19] and two new ent-labdane diterpenoid glycosides were isolated from the aerial parts.[20]

Mechanisms of Action

Hepatoprotective Effects

A. paniculata is extensively used as a hepatostimulant and hepatoprotective agent in Indian systems of medicine.[21] *A. paniculata* is also an ingredient in several polyherbal preparations used as hepatoprotectants in India,[22] one of which has been reported as efficacious in chronic hepatitis B virus infection.[23] Very few studies on the effects of crude extracts of *A. paniculata* on liver function are available. Most studies for hepatic effects have been conducted on either andrographolide or other purportedly active principles.

Shukla et al reported significant choleretic effects of andrographolide in conscious rats and anesthetized guinea pigs. The protection of andrographolide against acetaminophen-induced reduction in volume and contents of bile was better than that produced by silymarin.[24] Multiple-dose pretreatment with arabinogalactan proteins and andrographolide was protective against ethanol-induced hepatotoxicity in mice and was deemed comparable to the efficacy of silymarin.[25] Choudhury and Poddar reported that oral pre- and post-treatment of adult rats with an extract of *A. paniculata* was protective against ethanol-induced increase in serum transaminases. Administration of the extract to normal adult rats in single and multiple doses for seven and 15 consecutive days did not significantly affect serum transaminases.[26]

A comparative study on the effect of leaf extract or andrographolide on carbon tetrachloride (CCl_4)-induced hepatic microsomal lipid peroxidation revealed a protective effect of a single oral dose of the extract and of andrographolide. However, high concentration CCl_4-induced microsomal lipid peroxidation *in vitro* was completely protected by the extract but not by andrographolide, indicating that the hepatoprotective effect is not solely due to the presence of andrographolide.[27] Hepatoprotective effects of the crude alcohol extract of leaves against CCl_4-induced liver damage have also been reported by Rana and Avadhoot.[28]

Handa and Sharma compared andrographolide, methanol extract of the whole plant containing equivalent amounts of andrographolide, and an andrographolide-free methanol extract against CCl_4-induced liver damage in rats. The CCl_4-induced increases in serum transaminases, serum alkaline phosphatase, serum bilirubin, and hepatic triglycerides were inhibited by 48.6-, 32- and 15 percent, for andrographolide, methanol extract, and andrographolide-free methanol extract, respectively. Since all three treatments resulted in improvement in liver histology,[29] a hepatoprotective role of *A. paniculata* constituents other than andrographolide is suggested and corroborates the observation made by Choudhury and Poddar.[27]

The CCl_4-induced increase in pentobarbitone-induced sleep time in mice is also completely normalized by andrographolide. The effects of intraperitoneal (i.p.) pretreatment for three consecutive days with andrographolide on CCl_4- or tert-butyl hydroperoxide-induced hepatotoxicity in mice were compared with two other diterpenes – andrographiside and neoandrographolide. Both compounds showed a greater protective effect than andrographolide. The protection by andrographiside and neoandrographolide was comparable to silymarin, and neoandrographolide normalized glutathione levels.[30]

Trivedi et al observed protection by both the crude extract of *A. paniculata* and andrographolide against reduced activities of hepatic antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase), depletion of hepatic glutathione, and increased activities of hepatic γ-glutamyl transpeptidase, glutathione-S-transferase, and lipid peroxidase caused by hexachlorocyclohexane in mice.[31] Oral or i.p. pretreatment with andrographolide was also protective against galactosamine-induced liver damage in rats and prevented changes in biochemical parameters and liver histology. Similar protection was observed when rats were treated with andrographolide post-acetaminophen challenge,[32] and on an *ex vivo* preparation of isolated rat hepatocytes.[33]

Various extracts and constituents of *A. paniculata* were used in the experiments mentioned in this subsection. All showed hepatoprotective effects. *A. paniculata* also showed benefits against liver damage caused by agents with different hepatotoxic mechanisms, suggesting *A. paniculata* and its constituents are not agent-specific and might have broad-spectrum hepatoprotective effects. More research is needed to establish the identity of the most effective component(s) for hepatoprotection. Large, multicenter, clinical studies are warranted to determine whether *A. paniculata* is efficacious in patients with liver diseases of various origins.

Effects on Hepatic Metabolizing Enzymes

Drug-herb and drug-nutrient interactions can adversely influence the clinical response to treatment. Therefore, the effect of herbal and nutrient compounds on hepatic metabolic enzymes that influence drug pharmacokinetics is an area of interest in modern medicine. Singh et al reported that an 80-percent hydroalcohol extract (50 and 100 mg/kg/day for 14 days) of *A. paniculata* to mice significantly increased the levels of acid-soluble sulfhydryl content, cytochrome P450 (CYP450), cytochrome P450 reductase, cytochrome b5 reductase, glutathione S-transferase, and superoxide dismutase at both doses; while significant increases in the levels of catalase, glutathione peroxidase, and glutathione reductase were observed only at higher doses.[34] Both aqueous and alcoholic extracts of *A. paniculata* are reported to significantly increase the activities of CYP1A1 and CYP2B without affecting the total hepatic CYP450 contents in ICR male mice.[35] Andrographolide significantly induced CYP1A1 and CYP1A2 mRNA expression in cultures of mouse hepatocytes and acted synergistically with CYP1A inducers.[36] *A. paniculata* extract has recently been reported to noncompetitively inhibit CYP1A2 and CYP2C in rat and human liver microsomes and competitively inhibit CYP3A4 in human microsomes; whereas, andrographolide was found to be a weak inhibitor of rat CYP2E1 only.[37] Similar effects of the extract and andrographolide on CYP2C and CYP3A in rat and human hepatocyte cultures have been observed.[38] Existing evidence is not sufficient to draw any conclusions on drug-herb interactions. More extensive studies on hepatic metabolizing enzymes should be conducted in healthy humans and in humans taking medications that are susceptible to pharmacokinetic alterations by these inducible hepatic enzymes.

Antimicrobial and Antiparasitic Effects

A. paniculata has been extensively used to treat a variety of conditions of infectious origin in traditional systems of medicine. Modern research has investigated it for activity against various bacteria, viruses, and parasites. Crude powder suspended in water was reported to be devoid of *in vitro* antibacterial activity against Salmonella, Shigella, *Escherichia coli*, gram A Streptococci, and

Staphylococcus aureus, even at a concentration of 25 mg/mL crude powder. Administration of a single oral dose of powder, up to 6 g, to healthy volunteers in a randomized crossover manner or daily administration of 0.12-24 g/kg body weight to rats for six months also failed to show any *ex vivo* antibacterial activity.[39] Singha et al reported significant antibacterial activity of an aqueous extract and attributed it to the combined effect of andrographolides and arabinogalactan proteins.[40] A similar conclusion was reached by Zaidan et al who found crude aqueous extract of leaves exhibit significant antimicrobial activity against gram-positive *S. aureus*, methicillin-resistant *S. aureus* (MRSA), and gram-negative *Pseudomonas aeruginosa*, but had no activity against *Escherichia coli* or *Klebsiella pneumoniae*.[41] The ethanol extract was also devoid of significant activity against enterohemorrhagic strains of *E. coli*.[42]

Andrographolide, neoandrographolide, and 14-deoxy-11,12-didehydroandrographolide are reported to be viricidal against herpes simplex virus 1 (HSV-1) without having any significant cytotoxicity at viricidal concentrations.[43]

The alcohol extract of the rhizome was reported to possess significant *in vitro* activity against *Ascaris lumbricoides*.[44] The chloroform extract completely inhibited malarial parasitic growth within 24 hours of incubation at a concentration of 0.05 mg/mL. The same inhibition was achieved in 48 hours with methanol extract at a concentration of 2.5 mg/mL.[45] Mishra et al found that a methanol extract significantly inhibited *Plasmodium falciparum* at a 50-percent inhibitory concentration (IC_{50}) of 7.2 µg/mL.[46] The four xanthones – 1,8-dihydroxy-3,7-dimethoxyxanthone, 4,8-dihydroxy-2,7-dimethoxyxanthone, 1,2-dihydroxy-6,8-dimethoxyxanthone, and 3,7,8-trimethoxy-1-hydroxy-xanthone – isolated from the roots of the plant, also showed *in vitro* anti-malarial activity against *Plasmodium falciparum* and *in vivo* activity in Swiss albino mice infected with *Plasmodium berghei*.[47] The same xanthones also exhibited antiprotozoal activity against *Trypanosoma brucei*, *Trypanosoma cruzi*, and *Leishmania infantum*.[48] Water decoction of the leaves exhibited filaricidal activity, both *in vitro* and in dogs.[49]

Clinical relevance of these studies is inconclusive since results are predominantly *in vitro* or *ex vivo*. Many of the *in vitro* results obtained were also achieved at concentrations that may not be clinically feasible.

Cardiovascular Effects

Aqueous extract of *A. paniculata* produced a dose-dependent fall in systolic blood pressure of both spontaneously hypertensive rats (SHRs) and normotensive Wistar-Kyoto rats, with a corresponding significant decrease in plasma angiotensin converting enzyme (ACE) activity and lipid peroxidation in kidneys in extract-treated SHRs. The decreases in ACE activity and lipid peroxidation were not significantly altered in normotensive Wistar-Kyoto rats, an indication that suggests its hypotensive effect in hypertensive and normotensive rats is not mediated through identical mechanisms.[50] The hypotensive effect of n-butanol and aqueous fractions of the crude water extract is antagonized or attenuated by phentolamine, hexamethonium, pyrilamine, and cimetidine, but not by propranolol, atropine, or captopril.[51] However, the fall in mean arterial pressure produced by 14-deoxy-11, 12-didehydroandrographolide (DDA), one of the three active diterpenoids, in anesthetized Sprague-Dawley rats was attenuated in the presence of propranolol, hexamethonium, and captopril. DDA also antagonized the positive chronotropic effect of isoproterenol on the isolated rat right atria in a non-competitive and dose-dependent manner.[52] Hypotensive and negative chronotropic effects of DDA have been corroborated by a recent study that suggested that vascular smooth muscle is the major site of hypotensive activity of DDA and high-DDA extracts.[53]

Several studies investigated the effect of water extract and active constituents of *A. paniculata*, both pre- and post-experimental myocardial infarction (MI), in animals. A water extract was administered intravenously one hour after MI in dogs. Treatment restricted the infarct size and produced a milder core ischemic area than in control dogs; similar results were also observed with flavones extracted from the root.[54,55] Experimental myocardial ischemia-reperfusion injury in dogs results in ultrastructural changes in the ischemic region with an increase in Ca^{2+} and reduced superoxide dismutase, Ca^{2+}-ATPase, and Na^{+}-K^{+}-ATPase activities. Treatment with an extract of *A. paniculata* prevented Ca^{2+} overloading of the ischemic region and the fall in enzyme activities.[56,57] A refined extract (API0134) administered intravenously 45 min post-ischemia induction prevented increase in the left ventricle end-diastolic pressure and preserved relatively normal cardiac output and rhythm in dogs with experimental ischemia-reperfusion myocardial

injury.[58] Andrographolide pretreatment of rat cardiomyocytes is reported to protect them against hypoxia/reoxygenation injury in a time-dependent manner. This effect was associated with upregulation of cellular reduced glutathione (GSH) level and antioxidant enzyme activities.[59]

Wang and Zhao studied the effects of *A. paniculata* on restenosis after experimental balloon angioplasty. Pretreatment with *A. paniculata* extract prevented atherosclerotic iliac artery stenosis in rabbits produced by de-endothelialization and high cholesterol diet. Restenosis after experimental angioplasty in the stenosed arteries was also significantly prevented. The extract inhibited cell growth and DNA synthesis in a dose-dependent manner. This is similar to the mechanism by which stents are coated with drugs that inhibit cell division.[60,61]

Aqueous extract, andrographolide, and DDA inhibit thrombin-induced platelet aggregation in time- and concentration-dependent manners. Extracts with a higher DDA concentration have less inhibitory activity than extracts with lower DDA concentration, indicating the presence of other compounds in the water extract with antiplatelet aggregation activity.[62] Andrographolide inhibits platelet-activating factor (PAF)-induced platelet aggregation in a dose-dependent manner without affecting the biosynthesis of eicosanoids.[7]

An extract of *A. paniculata* significantly inhibited *ex vivo* ADP-induced platelet aggregation in 63 patients with cardiac and cerebral vascular diseases three hours after administration. Thirty-three of these patients who were observed for platelet aggregation after one week experienced even more significant effects. Serotonin release from platelets was significantly reduced in 20 extract-treated volunteers, while the plasma serotonin levels remained unchanged.[63]

Reports regarding hypotensive activity of extracts and some constituents are consistent. Further studies are needed to establish the mechanisms of action, constituents with hypotensive actions, constituent interactions with blood pressure-lowering medications, and clinical efficacy in hypertensive humans. The results of cardiovascular and platelet antiaggregation studies require further exploration in clinical situations.

Antioxidant and Anti-inflammatory Activities

Antioxidant and anti-inflammatory activities of *A. paniculata* and its constituents have been reported by various investigators. Das et al reported that nicotine-induced inhibition of mitochondrial electron chain complexes and the resultant increase in nitric oxide (NO) in different parts of rats' brains was prevented by simultaneous treatment with the water and ethanol extracts of *A. paniculata* or andrographolide; the water extract exhibited greater antioxidant activity than the ethanol extract.[64] Phytochemical analysis showed higher flavonoid but lower phenol contents in water extract than in ethanol extract.[65] Verma and Vinayak compared the antioxidant effects of the aqueous extract on liver defense systems in lymphoma-bearing AKR mice. The aqueous extract significantly increased the activities of catalase, superoxide dismutase, and glutathione-S-transferase enzymes and reduced lactate dehydrogenase activity.[66] A methanol extract inhibited formation of reactive oxygen species (ROS) *in vitro* and completely inhibited carrageenan-induced inflammation.[67] Andrographolide pretreatment significantly attenuates accumulation of phorbol-12-myristate-13-acetate (PMA)-induced formation of ROS and N-formyl-methionyl-leucyl-phenylalanine (fMLP)-induced adhesion of rat neutrophils.[68] However, PMA-induced formation of ROS and fMLP-induced adhesion and transmigration of peripheral human neutrophils was only partially reversed by andrographolide. This study suggests that prevention of ROS production was partly mediated by the direct activation of protein kinase C by PMA and partly mediated by down-regulation of surface Mac-1 expression, an essential integrin for neutrophil adhesion and transmigration, respectively.[69]

Excessive amounts of NO and prostaglandin E_2 (PGE_2), due to expression of inducible isoforms of nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) from activated macrophages, play a significant role in inflammatory processes. Lipopolysaccharide (LPS) stimulates and promotes secretion of pro-inflammatory cytokines from macrophages and causes induction of iNOS, resulting in increased production of NO. Incubation of macrophages with methanol extract, andrographolide, and neoandrographolide inhibits LPS-stimulated NO production in a concentration-dependent manner.[70-73] Andrographolide-induced reduction of iNOS activity may be due to reduced expression of iNOS protein.[71,72] Andrographolide also fully restores the maximal contractile response of thoracic aorta to phenylephrine after incubation with LPS, and attenuates the fall in mean arterial blood pressure of anesthetized rats due to LPS.[71] Unlike andrographolide, neoandrographolide was also effective *ex vivo* in suppressing NO production

when macrophages were collected after oral administration of neoandrographolide and subjected to LPS stimulation.[69] Andrographolide inhibited LPS-induced increase in tumor necrosis factor-alpha (TNF-α) and granulocyte-macrophage colony stimulating factor.[74] Neoandrographolide also inhibits PGE_2 synthesis[73] and TNF-α in LPS-stimulated macrophages, and its oral administration to mice significantly suppresses dimethylbenzene-induced ear edema and acetic acid-induced vascular permeability.[75] API0134, a refined extract of *A. paniculata*, also significantly reduces activities of lipid peroxide and endothelin, while the activities of NO, cGMP, and superoxide dismutase are significantly enhanced in experimental atherosclerotic rabbits.[76]

Antihyperglycemic and Hypoglycemic Effects

Water extract of *A. paniculata* significantly prevents orally administered glucose-induced hyperglycemia in nondiabetic rabbits without affecting epinephrine-induced hyperglycemia. Chronic administration of the extract for six weeks also showed no effect on fasting blood glucose level.[77] However, ethanol extract, administered orally twice daily for 14 days to streptozotocin-induced diabetic rats significantly reduced fasting serum glucose and increased body weight in a dose-dependent manner. The extract also significantly lowered levels of thiobarbituric acid-reactive substances in liver and kidney compared to vehicle-treated rats, while significantly increasing the activity of superoxide dismutase and catalase enzymes and hepatic glutathione concentrations in diabetic rats.[78] An ethanol extract at a dose of 400 mg/kg body weight twice daily for two weeks to diabetic rats produced a 49.8-percent reduction in fasting serum triglyceride levels. This was greater than the 27.7-percent decline achieved with 500 mg/kg body weight metformin twice daily for 14 days.[79] An aqueous extract (50 mg/kg body weight) given to streptozotocin-diabetic rats resulted in a 52.9-percent decrease in blood glucose levels. Freeze-dried material decreased blood glucose by 61.8 percent at a lower dose of 6.25 mg/kg body weight.[80] Similar results were obtained by Dandu and Inamdar with oral administration of an aqueous extract of *A. paniculata* leaves. A dose of 400 mg/kg lowered blood glucose level of streptozotocin-induced animals and increased activity of superoxide dismutase and catalase. Oral administration of the decoction also significantly reduced blood glucose levels in alloxan-induced diabetic rats, and reduced food and water intake compared to vehicle-treated diabetic controls.[81] Extended mean estrous cycles (eight days) was reduced to five days in treated diabetic rats.[82]

Andrographolide appears to dose-dependently reduce plasma glucose concentration in streptozotocin-induced diabetic rats and normal rats, with a more marked effect in normal rats than in diabetic rats.[83] This is a significant difference from the water extract, which did not show a glucose-lowering effect in one study of normoglycemic rats.[81] Andrographolide also attenuates the increase in plasma glucose in response to an intravenous glucose challenge in normal rats and enhances the uptake of radioactive glucose by isolated soleus muscle of streptozotocin-diabetic rats in a concentration-dependent manner. Repeated intravenous administration of andrographolide in diabetic rats for three days resulted in an increase in mRNA and protein levels of glucose transporter (GLUT4) in the soleus muscle, an indication that the glucose-lowering effect of andrographolide could be due to better glucose utilization by skeletal muscle.[83] However, after *in vitro* experiments, Wibudi et al concluded that the hypoglycemic effect of *A. paniculata* is due to insulin release from pancreatic β-cells through ATP-sensitive potassium channels, similar to other insulinotropic antidiabetic agents.[84] *In vitro* experiments conducted by Subramanian et al suggested that inhibition of alpha-glucosidase and alpha-amylase enzyme could be the mechanism by which the ethanol extract of *A. paniculata* and andrographolide produce hypoglycemic effect.[85]

Available evidence suggests that the hypoglycemic and antihyperglycemic activities of the extract and andrographolide may involve different mechanisms in normal and diabetic conditions. Water extract seems to be a more suitable candidate for further studies as it does not affect fasting blood glucose levels of nondiabetic animals. Identification of blood glucose-lowering constituents in both water and ethanol extracts may be of value.

Effects on Reproductive Systems

A number of animal studies report an effect of *A. paniculata* on male and female reproduction. Early reports of oral administration of powdered stem indicated an antifertility effect in male Wistar mice, but no impact on fertility in female mice.[86,87] In has also been reported that administration of *A. paniculata* resulted in abortion in pregnant rabbits.[6] Intraperitoneal injection of the decoction of aerial parts to female albino mice was reported

to prevent implantation and caused abortion at different gestation periods. Early pregnancy was also terminated by intramuscular, subcutaneous, and intravenous administration. Administration of progesterone or luteinizing hormone-releasing hormone completely or markedly antagonized the abortifacient effects, indicating an interference with progesterone activity as a potential mechanism for this abortifacient effect. In addition, the herb is reported to suppress growth of human placental chorionic trophoblastic cells *in vitro*.[6]

Zoha et al fed female mice sun-dried Andrographis powder at a dose of 2 g/kg body weight/day for six weeks. When they were mated with untreated males of proven fertility, pregnancy was inhibited in 100 percent of the animals. Conversely, more than 95 percent of untreated female mice in the control group became pregnant when mated with males in a similar fashion.[88] Akbarsha et al administered dry leaf powder to male albino rats (20 mg daily for 60 days). They reported inhibition of spermatogenesis, degenerative changes in the seminiferous tubules, regression of Leydig cells, and regressive and/or degenerative changes in the epididymis, seminal vesicle, ventral prostate, and coagulating glands.[89] Andrographolide also produced similar results when orally administered to male Wistar albino rats for 48 days. Sperm count and sperm motility were decreased and sperm abnormalities were noted.[90] However, Burgos et al found no testicular toxicity in male Sprague Dawley rats after treatment with a standardized dried extract in doses of up to 1,000 mg/kg daily for 60 days. Their analysis was based on testicular weight and histology, ultrastructural analysis of Leydig cells, and testosterone levels.[91] Extract of *A. paniculata* also did not affect the progesterone levels in pregnant rats when administered orally in doses of 200, 600, and 2,000 mg/kg daily during the first 19 days of pregnancy.[92] Burgos et al reported that dried extract of *A. paniculata* induces uterine relaxation by blocking voltage-sensitive calcium channels.[93] A phase I clinical study on Kan-Jang (a combination of *A. paniculata* and *Eleutherococcus senticosus*) reported no significant negative effects on sperm quality and fertility of healthy adult males.[94]

Existing evidence is too inconsistent, with some findings directly contradicting others, to reach any definitive conclusion about the reproductive effects of *A. paniculata*. The existing evidence does suggest that *A. paniculata* is unlikely to be an effective form of birth control. Further studies on short- and long-term effects on fertility are warranted.

Clinical Studies

Dysentery/Gastroenteritis

Studies conducted in China have reported therapeutic value in acute bacillary dysentery and gastroenteritis. Ethanol extract tablets reportedly cured 88.3 percent of acute bacillary dysentery and 91.3 percent of acute gastroenteritis cases.[6] Andrographolide administration was reported to cure 91 percent of acute bacillary dysentery cases.[6] The same cure rate (91.1%) was achieved with a compound tablet containing andrographolide and neoandrographolide (at a ratio of 7:3) in cases of bacillary dysentery. This was reported to be higher than cure rates obtained with furazolidine or chloramphenicol.[6]

Infectious Diseases

A. paniculata or its constituents have been used to treat cases of leptospirosis, pulmonary tuberculosis (especially the exudative type), tuberculous meningitis, and acute pyelonephritis.[6] In acute pyelonephritis, the results were reported to be similar to those obtained with nitrofurantoin, but with fewer adverse effects.[6] Intra-arterial or retrograde intravenous injections of the herb were reportedly effective in thromboangiitis obliterans, especially of "heat toxic type."[6] Ten cases of viper bites were reportedly cured in 3-5 days by a compound formula that had *A. paniculata* as the chief constituent.[6]

A phase I, dose-escalating clinical trial of andrographolide was conducted in 13 HIV-positive patients and five HIV-negative healthy volunteers. The planned protocol was to start with a dose of 5 mg/kg body weight for the first three weeks, increase to 10 mg/kg body weight for three weeks, and then to 20 mg/kg body weight for a final three weeks. Andrographolide administration significantly improved the CD4+ lymphocyte count from a baseline mean of 405 cells/mm^3 to 501 cells/mm^3 in HIV-positive patients. There was no statistically significant change in mean plasma HIV-1 RNA levels. This trial was stopped after six weeks because of adverse events.[13]

A. paniculata has been used for uncomplicated upper respiratory tract infections (URTIs). There appears to be differences in the degree of therapeutic effect based upon the kind of preparation used and duration of treatment. Pills (made from the whole powdered plant with water) and tablets (made from the water extract of the herb) produced aggregate effective rates of 88 percent and 61 percent in URTI, respectively.[6] In a randomized, double-blind, controlled study, Thamlikitkul et al

gave *A. paniculata* at a dose of 6 g/day for seven days to 152 Thai adults suffering from pharyngotonsillitis. Efficacy was comparable to acetaminophen in relieving symptoms of fever and sore throat.[95] A study of 158 adult patients suffering from common cold used a standardized *A. paniculata* dried extract SHA-10 (1,200 mg/day) for five days. The extract significantly decreased the intensity of the symptoms of tiredness, sleeplessness, sore throat, and nasal secretion, starting from the second day of treatment.[96] Self-limiting side effects were reported in 20 percent of patients from both groups in the former study and no significant adverse effects were reported in the latter study.

A commercial preparation consisting of a standardized extract of *A. paniculata* in a fixed combination with *Eleutherococcus senticosus* (Kan Jang) has been tested in uncomplicated URTIs. Two randomized, double-blind, placebo-controlled parallel group trials were conducted in Sweden. One was a pilot study that involved 46 patients who were treated with Kan Jang three times daily for a minimum of three days and a maximum of eight days; the other was a phase III study of 179 patients for three days. Patients' self-evaluation in regard to muscle aches, cough, sore throat, headache, nasal discharge, eye symptoms, and fever served as the primary outcome measures. Throat symptom relief was highly significant in treated groups compared to placebo-treated groups in both studies.[97] In a similar Armenian study, 95 patients with acute URTIs, including sinusitis, were treated with Kan Jang for five days, while a group of 90 patients served as control. A highly significant improvement in headache, nasal and throat symptoms, and general malaise was reported in the treated groups, including the sinusitis subgroups, while cough and eye symptoms did not differ significantly from the placebo group.[98]

Effects of Kan Jang on uncomplicated respiratory disease have also been studied in children (ages 4-11 years). In a three-arm study, a group treated with standard common cold treatment served as a control. In two groups, Kan Jang or an Echinacea preparation was added as an adjunct to standard treatment for 10 days. Patients receiving Kan Jang as adjunct to standard therapy at an early stage of the common cold showed less severe symptoms, especially nasal congestion and secretions, faster recovery, and a significantly lower need for standard medication.[99] Two systemic reviews of randomized, controlled trials concluded that *A. paniculata* was a safe and efficacious alternative treatment for uncomplicated URTIs compared to placebo.[100,101]

The results from these Kan Jang trials, in both adults and children, cannot be attributed exclusively to the effects of *A. paniculata*, since it was given in combination with *E. senticosus*. The majority of other clinical trials have been published in Chinese journals and lack sufficient details to determine actual efficacy, especially since many conditions studied are self-limiting. More clinical research is required before *A. paniculata* can be deemed efficacious for conditions other than URTI.

Toxicity and Dosing

The LD_{50} of the alcohol extract, obtained by cold maceration, is 1.8 g/kg.[28] The LD_{50} of andrographolide (yield 0.78% w/w from whole plant) in male mice through intraperitoneal route is 11.46 g/kg.[29]

In the study on HIV-positive patients a dose of 1,500-2,000 mg of andrographolides was given daily for six weeks. Side effects were common and the study was discontinued early despite some improvements in CD4+ counts.[13]

Until definitive information on *A. paniculata* and its constituents on reproduction is available, it would be prudent for both men and women to avoid this herb during desired conception and for women during pregnancy.

The majority of studies for common colds and URTI used a patented product – Kan Jang – which combines *A. paniculata* and *E. senticosus*. Andrographis used in this product is standardized to contain 4-6 percent andrographolides and the dose used provided anywhere from 60-72 mg per day (low range) up to about 300 mg per day (highest dose). Existing evidence suggests that best results might be obtained if taken within the first 24 hours of URTI symptoms.

Conclusions and Other Potential Uses

The hepatoprotective effects of pretreatment with various extracts and constituents of *A. paniculata* are very consistent. Moreover, its inclusion in effective polyherbal formulations for liver ailments not amenable to any modern intervention lends support to its potential effectiveness. Before definitive conclusions can be drawn, it would be prudent to study the effects of *A. paniculata* or its constituents under experimental conditions of post-hepatic damage to determine if and how they reverse the pathological changes and which form is the most effective. More research is needed to determine the effects of this

herb on liver-metabolizing enzymes and drug interactions.

Inconsistency in *in vitro* antibacterial effects could be due to several factors, the variation of the constituents in the material tested being the prime suspect. The negative antibacterial results have been reported from Thailand by Leelarasamee et al[39] and Voravuthikunchai and Limsuwan,[42] while the results reported from India[40] and Malaysia[41] have been positive. Place and timing of collection of the plant, storage, and extraction conditions may all affect the constituents both qualitatively and quantitatively. It is imperative to establish the relationship of the activity with the presence of constituents in cases where a crude preparation is tested for it to be declared as possessing any antimicrobial activity.

The plant has shown some significant effects on blood pressure. Before *A. paniculata* can be used clinically in hypertensive conditions, further research must be conducted to expand the understanding of this plant and its constituents on blood pressure and its regulation. The same is true in other cardiovascular conditions where pharmacological studies have suggested potential effectiveness, such as in restricting the infarct size,[54,55] maintaining cardiac function under experimental cardiac ischemic conditions,[58] preventing platelet aggregation,[63] and preventing restenosis after balloon angioplasty.[60,61]

Significant antihyperglycemic activity in diabetic rats has been observed with both water and alcohol extracts. The alcohol extract reduced the serum triglyceride levels highly significantly, and better than metformin treatment (an extensively used antidiabetic drug).[79] Both extracts increased activities of antioxidant enzymes, a mechanism suggested as a potential glucose lowering mechanism.[78,81] Better glucose utilization via upregulation of GLUT4[83] and increased insulin release[84] have also been proposed as mechanisms for the antihyperglycemic effect. This activity requires further exploration.

Existing evidence supports *A. paniculata*'s role in the treatment of URTI. It might also have a role in accelerating the course of other self-limited infections.

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