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Review Article

A REVIEW ON KING OF BITTER (KALMEGH)

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ABSTRACT

Andrographis paniculata nees (Acanthaceae) is a medicinal plant traditionally used for the treatment of anti-inflammatory, antibacterial, antioxidant, antiparasitic, antispasmodic, antidiabatic, anti carcinogenic, antipyretic, antidiarrhoeal, hepatoprotective, nematocidal, anti-HIV and several infectious diseases ranging from malaria to dysentery. The plant is widely used in ayurvedic and homeopathic systems of medicines. The medicinal value of this plant is due to the presence of active ingredients *viz* andrographolide and neoandrographolide which are derivatives of diterpenoids. It prevents oxidative damage and inhibits binding to toxic metabolites to DNA.

Keywords *Andrographis paniculata*, traditional uses, pharmacology

NTRODUCTION

Andrographis paniculata is a herbaceous plant in the family *Acanthaceae*, native to India and Sri Lanka. It is widely cultivated in Southern and Southeastern Asia, where it is used to treat infections and some diseases, often being used before antibiotics were created. Mostly the leaves and roots were used for medicinal purposes.

Andrographis paniculata is an erect annual herb extremely bitter in taste in all parts of the plant body. The plant is known in north-eastern India as *Maha-tita*, literally "king of bitters", and known by various vernacular names. As an Ayurveda herb it is known as *Kalmegh* or *Kalamegha*, meaning "dark cloud". It is also known as *Bhui-neem*, meaning "neem of the ground", since the plant, though being a small annual herb, has a similar strong bitter taste as that of the large Neem tree (*Azadirachta indica*). In Malaysia, it is known as *Hempedu Bumi*, which literally means 'bile of earth' since it is one of the bitterest plants that are used in traditional medicine. The genus *Andrographis* consists of 28 species of small annual shrubs essentially distributed in tropical Asia. Only a few species are medicinal, of which *Andrographis paniculata* is the most popular. *Andrographis paniculata* grows erect to a height of 30–110 cm in moist, shady places. The slender stem is dark green, squared in cross-section with longitudinal furrows and wings along the angles. The lance-shaped leaves have hairless blades mea ruing up to 8 centimeters long by 2.5 wide. The small flowers are borne in spreading racemes. The fruit is a capsule around 2 centimeters long and a few millimeters wide. It contains many yellow-brown seeds. *Andrographis paniculata* is distributed in tropical Asian countries, often in isolated patches. It can be found in a variety of habitats, such as plains, hillsides, coastlines, and disturbed and cultivated areas such as roadsides, farms, and wastelands. Native populations of *Andrographis paniculata* are spread throughout south India and Sri Lanka which perhaps represent the centre of origin and diversity of the species. The herb is an introduced species in northern parts of India, Java, Malaysia, Indonesia, the West Indies, and elsewhere in the Americas. The species also occurs in Hong Kong, Thailand, Brunei, Singapore, and other parts of Asia where it may or may not be native. The plant is cultivated in many areas, as well. Unlike other species of the genus, *Andrographis paniculata* is of common occurrence in most places in India, including the plains and hilly areas up to 500 m, which accounts for its wide

use. Since time immemorial, village and ethnic communities in India have been using this herb for treating a variety of ailments.

CLASSIFICATION OF ANDROGRAPHIS PANICULATA

Kingdom:Plantae
Order:Lamiales
Family:Acanthaceae
Genus:Andrographis
Species:A.paniculata

COMMON NAME - Kalmegh, kirayat, bhunimba

LIST OF VERNACULAR NAMES OF *ANDROGRAPHIS PANICULATA* NEES

Language	Common name
Sanskrit	Kālamegha (□□□□□□), Bhūnimba (□□□□□□□□)
Hindi	Kirayat
Assamese	Chiorta
Bengali	Kālmegh
Oriya	Bhuinimba
English	Green chirayta, king of bitters, India Echinacea
Gujarati	Kariyatu
Tamil	Nilavembu, Sirunangai, Siriyanangai
Kannada	Nelaberu
Telugu	Nelavemaa
Marathi	Oli-kiryata
Persian	Naine-havandi
Chinese	Chuan Xin Lian
Arabic	Quasabhuva

TRADITIONAL USES

Andrographis paniculata has been reported as having antibacterial, antifungal, antiviral, choleretic,hypoglycemic, hypocholesterolemic, adaptogenic, anti-inflammatory, emollient, astringent, diuretic, carminative, anthelmintic, antipyretic, gastric and liver tonic. 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. Juice or an infusion of fresh leaves is given to infants to relieve griping, irregular bowel habits, and loss of appetite. 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. In China, the herb derived from the leaves or aerial parts of Andrographis *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. *Andrographis paniculata* is used for the treatment of pharyngolaryngitis, diarrhea, dysentery, and cough with thick sputum, carbuncle, sores, and snake bites. 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.

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

PHYTOCONSTITUENTS

Andrographis paniculata contains diterpenes, lactones and flavonoids. Flavonoids mainly exist in the root, but have also been isolated from the leaves. Aerial parts contain alkanes, ketones, and aldehydes and the bitter principles in the leaves were due to presence of the lactone andrographolide 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. A diterpene glucoside (deoxyandrographolide- 19beta-D-glucoside) has been detected in the leaves 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. Two flavonoids identified as 5, 7, 2', 3'-tetramethoxyflavanone and 5-hydroxy-7, 2', 3'-trimethoxyflavone were isolated from the whole plant, while 12 new flavonoids and 14 diterpenoids have been reported from the aerial parts. Two new flavonoid glycosides and a new diterpenoids (andrographic acid) were recently reported, and two new ent-labdane diterpenoids glycosides were isolated from the aerial parts.

PHARMACOLOGY

HEPATOPROTECTIVE EFFECTS

Andrographis paniculata is extensively used as a hepatoprotective agent in Indian systems of medicine. *Andrographis paniculata* is also an ingredient in several polyherbal

preparations used as hepatoprotectants in India, one of which has been reported as efficacious in chronic hepatitis B virus infection. Most studies for hepatic effects have been conducted. *Shukla et al* reported significant choleretic effects of andrographolide in rats and guinea pigs. "e protection of andrographolide against acetaminophen-induced reduction in volume and contents of bile was better than that produced by silymarin. 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.

Chowdhury and Poddar reported that oral pre- and post-treatment of adult rats with an extract of *Andrographis paniculata* was protective against ethanol-induced increase in serum transaminase. Administration of the extract to normal adult rats in single and multiple doses for seven and 15 days did not significantly affect serum transaminase. A comparative study on the effect of leaf extract or andrographolide on carbon tetrachloride (CCl4)-induced hepatic microsomal lipid peroxidation revealed a protective effect of a single oral dose of the extract and of andrographolide. However, high concentration CCl4-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. Hepatoprotective effects of the crude.

Handa and Sharma compared andrographolide, methanol extract of the whole plant containing equivalent amounts of andrographolide, and an andrographolide-free methanol extract against CCl4-induced liver damage in rats. "e CCl4-induced increases in serum transaminase, 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.

Trivedi et al observed protection by both the crude extract of *Andrographis 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 glutamyl transpeptidase, glutathione-S-transferase, and lipid peroxidase caused by hexachlorocyclohexane in mice. Oral or ip. 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 and on an *ex vivo* preparation of isolated rat hepatocytes. 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.

ANTIMICROBIAL AND ANTI-PARASITIC EFFECTS

Andrographis paniculata has been extensively shows antimicrobial and antiparasitic activities. Such as bacteria, viruses, and parasites. Singha et al reported significant antibacterial activity of an aqueous extract and attributed it to the combined effect of andrographolides and arabinogalactan proteins. 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* and gram-negative *Pseudomonas aeruginosa*, but had no activity against *Escherichia coli* or *Klebsiella pneumoniae*. 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. Alcoholic extract of the rhizome was reported to possess significant *in vitro* activity against *Ascaris lumbricoides*.44 and chloroform extract completely inhibited malarial parasitic growth within 24 hours of incubation at a concentration of 0.05 mg/mL. Same inhibition was achieved in 48 hours with methanol extract at a concentration of 2.5 mg/mL.

Mishra et al found that a methanol extract significantly inhibited *Plasmodium falciparum* at a 50-percent inhibitory concentration (IC50) of 7.2 µg/mL.46 "e 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*.

ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITIES

Antioxidant and anti-inflammatory activities 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. Phytochemical analysis showed higher flavonoid but lower phenol contents in water extract than in ethanol extract.

Verma and Vinayak compared the antioxidant effects of the aqueous extract on liver defense systems in lymphoma-bearing AKR mice. "e 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. However, PMA-induced formation of ROS and fMLP-induced adhesion and transmigration of peripheral human neutrophils was only partially reversed by andrographolide. "is 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 neutrophils adhesion and transmigration, respectively.69 Excessive amounts of NO and prostaglandin E2 (PGE2), due to expression of inducible isoforms of nitric oxide synthase 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. Andrographolide-induced reduction of iNOS activity may be due to reduced expression of iNOS protein. 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. 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. Andrographolide inhibited LPS-induced increase in tumor necrosis factor-alpha (TNF) and granulocyte-macrophage colony stimulating factor. Neoandrographolide also inhibits PGE2 synthesis and TNF-in LPS-stimulated macrophages, and its oral administration to mice significantly suppresses dimethylbenzene-induced ear edema and acetic acid-induced vascular permeability.

ANTIHYPERGLYCEMIC AND HYPOGLYCEMIC EFFECTS

Water extract of *Andrographis paniculata* significantly prevents orally administered glucose-induced hyperglycemia in non diabetic rabbits without affecting epinephrine-induced hyperglycemia. Chronic administration of the extract for six weeks also showed no effect on fasting blood glucose level. 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. "e 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. 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. it was greater than the 27.7-percent decline achieved with 500 mg/kg body weight Metformin twice daily for 14 days. 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. Similar results were obtained by Dandu and Inamdar with oral

administration of an aqueous extract of *Andrographis 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. Extended mean estrous cycles (eight days) were reduced to five days in treated diabetic rats. 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. It is a significant difference from the water extract, which did not show a glucose lowering effect in one study of normoglycemic rats. 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. However, after *in vitro* experiments, Wibudi et al concluded that the hypoglycemic effect of *Andrographis paniculata* is due to insulin release from pancreatic cells through ATP-sensitive potassium channels, similar to other insulin tropic antidiabatic agents. *In vitro* experiments conducted by Subramanian et al suggested that inhibition of alpha-glucosides and alpha-amylase enzyme could be the mechanism by which the ethanol extract of *Andrographis paniculata* and andrographolide produce hypoglycemic effect. 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 non diabetic 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 *Andrographis 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. In has also been reported that administration of *Andrographis paniculata resulted* in abortion in pregnant rabbits. Intraperitoneally 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*. 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. Akbarsha et al administered dry leaf powder to male albino rats (20 mg daily for 60 days) 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. 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. 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. Its analysis was based on testicular weight and histology, ultra structural analysis of Leydig cells, and testosterone levels. Extract of *Andrographis 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. Burgos et al reported that dried extract of *A. paniculata* induces uterine relaxation by blocking voltage-sensitive calcium channels. 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. Existing evidence is too inconsistent, with some findings directly contradicting others, to reach any definitive conclusion about the reproductive effects of *Andrographis paniculata*. "e 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.

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