

Pharmacological Activities of the Nelabevu/Bhunimba aka *Andrographis paniculata*

Abstract

Andrographis paniculata, commonly known as Nelabevu, Bhunimba, Chirayetah, Kalmegh, or Creat, is a plant with extensive traditional use in Asian medicines. Its historical application, particularly in conditions related to blood irregularities, has driven contemporary scientific investigations into its therapeutic potential. This review summarizes the diverse aspects of *Andrographis paniculata*'s traditional uses and modern applications, covering its effectiveness in respiratory infections, hepatoprotection, cardiovascular effects, antimicrobial and anti-inflammatory activities, hypoglycemic effects, and reproductive influences. The plant's active constituents, such as andrographolide, flavonoids, and diterpenoids, contribute to its pharmacological actions. However, critical evaluation and further research are essential to confirm its clinical benefits and mechanisms of action. The extensive range of its effects and the multiple active compounds highlight the plant's significance in modern herbal medicine and warrant continued exploration.

Keywords

Andrographis paniculata, Nelabevu, Bhunimba, traditional medicine, ayurvedic medicine, antibacterial, antifungal, antiviral, reproductive effects, phytoconstituents, flavonoids, clinical trials, herbal medicine.

Introduction

Andrographis paniculata, a valued component of traditional Asian medicine, is renowned for its role in treating various conditions [1,2]. It is particularly noted for its ability to purify blood, making it indispensable for managing conditions like skin eruptions, boils, scabies, and persistent fevers [1]. This plant's medicinal use mainly involves its aerial parts, which contain a diverse range of chemical compounds such as lactones, diterpenoids, flavonoids, and glycosides [1]. Clinical trials support its effectiveness in alleviating symptoms of uncomplicated upper respiratory tract infections [1].

While *A. paniculata* has been a staple in traditional healing systems [2], its benefits deserve careful evaluation due to the self-limiting nature of many conditions it addresses. This review highlights current scientific findings and emphasizes the need for comprehensive research to validate its therapeutic efficacy [3,4].

Known as "Chirayetah" and "Kalmegh" in Urdu and Hindi, this annual plant grows to 1 to 3 feet and is revered in Unani and Ayurvedic traditions [2]. Also known as "Creat" and "king of bitters," it thrives in India and across Asia, where it holds a significant place in traditional medicine [2].

Though primarily using the plant's aerial parts, historical records suggest the utilization of the whole plant or its roots for specific therapeutic purposes [2]. Traditional forms of consumption included infusion, decoction, or powder, either alone or in combination with other herbs [2]. Today, commercial preparations often focus on standardized whole-plant extracts, bridging tradition and modernity [2].

Given the self-limiting nature of many conditions traditionally treated with *A. paniculata*, it's essential to critically consider its claimed benefits [3,4]. This synthesis presents existing scientific knowledge and points toward areas deserving further exploration. The references provided serve as a foundation for understanding the healing potential of *Andrographis paniculata*.

Traditional Applications of *Andrographis paniculata* in Medicine

A. paniculata exhibits diverse benefits, including antibacterial, antifungal, and antiviral properties [3]. In Unani medicine, it serves as an aperient, anti-inflammatory, liver tonic, and more [1]. It addresses conditions like skin issues, fevers, irregular bowel habits, and debility [2,4,5].

In Chinese medicine, *A. paniculata* treats *pharyngolaryngitis*, diarrhea, snakebites, and more [6]. It dispels pathogenic heat and proves effective against infectious and non-infectious diseases [6].

Modern Uses

A fundamental contemporary application of *A. paniculata* revolves around its utilization in both preventing and treating the common cold. Notably, its antithrombotic actions point towards a potential advantage in addressing cardiovascular ailments [7]. Through extensive pharmacological and clinical investigations, promising prospects have emerged regarding its efficacy in conditions such as cancer [8-12] and HIV infections [13].

Phytoconstituents Composition

In *A. paniculata*, various phytoconstituents exist, including diterpenes, lactones, and flavonoids. Flavonoids are mainly in the roots but also in the leaves. Aerial parts contain alkanes, ketones, and aldehydes. Bitterness was attributed to andrographolide, but *kalmaghin* is another bitter component. China identified four lactones (Chuan Xin Lian A, B, C, D) from aerial parts. Leaves hold a diterpene glucoside (deoxyandrographolide 19beta-D-glucoside), six ent-labdane diterpenoids, and more. The whole plant yielded identified flavonoids. Recent findings include 12 new flavonoids, 14 diterpenoids, two flavonoid glycosides, a new diterpenoid (andrographic acid), and two ent-labdane diterpenoid glycosides from aerial parts [6,17-20].

Mechanisms of Operation

Hepatoprotective Effects

A. paniculata is widely used in Indian traditional medicine for its hepato-stimulant and hepatoprotective properties[21]. It's part of polyherbal formulations for hepatoprotection[22], even showing effectiveness against chronic hepatitis B[23].

Andrographolide, the main active compound, has significant choleric effects, surpassing silymarin in protecting against acetaminophen-induced bile reduction[24]. Combining arabinogalactan proteins and andrographolide provided hepatoprotection against ethanol-induced damage comparable to silymarin[25]. *A. paniculata* extract protected rats from ethanol-induced serum transaminase elevation[26], and it showed protection against hepatic lipid peroxidation induced by CCl₄[27]. Crude alcohol extracts from leaves also exhibited hepatoprotective effects against CCl₄-induced liver damage[28].

Studies showed that andrographolide, the methanol extract of the whole plant, and andrographolide-free methanol extract inhibited CCl₄-induced liver damage in rats, indicating *A. paniculata's* constituents beyond andrographolide play a hepatoprotective role[29]. Andrographolide exhibited protective effects against hepatotoxicity induced by various agents, comparable to or exceeding the effects of compounds like *andrographolide* and *neoandrographolide*[30]. Both *A. paniculata* and *andrographolide* provided protection against oxidative stress and liver damage in mice as indicated by studies[31-33].

The experiments used different extracts and components, all displaying hepatoprotective effects. *A. paniculata's* constituents seem to possess broad-spectrum hepatoprotective effects, warranting further research to determine the most effective component(s) and their efficacy in treating diverse liver diseases[21-33].

Influence on Hepatic Metabolic Enzymes

Investigating interactions between drugs, herbs, and nutrients that affect hepatic metabolic enzymes is crucial for treatment outcomes. An 80% hydroalcohol extract of *Andrographis paniculata* increased acid-soluble sulfhydryl content and levels of enzymes like cytochrome P450 (CYP450), cytochrome P450 reductase, and superoxide dismutase in rats[34]. Aqueous and alcoholic extracts boosted CYP1A1 and CYP2B activities without affecting total hepatic CYP450 content in male mice[35]. Andrographolide-induced CYP1A1 and CYP1A2 mRNA expression in mouse hepatocytes synergistically with CYP1A inducers[36]. A study noted noncompetitive inhibition of CYP1A2 and CYP2C, and competitive inhibition of CYP3A4 by *A. paniculata* extract in rat and human liver microsomes, while andrographolide weakly inhibited rat CYP2E1[37]. Similar effects were seen in rat and human hepatocyte cultures for CYP2C and CYP3A inhibition by both the extract and andrographolide[38]. Definitive conclusions about drug-herb interactions are lacking. Further research on hepatic metabolizing enzymes in healthy humans and those taking medications susceptible to pharmacokinetic changes by these enzymes is needed.

Antimicrobial and Antiparasitic Effects

Andrographis paniculata has historical use in traditional medicine for infectious conditions. Research has explored its

potential against bacteria, viruses, and parasites. Powdered crude extract in water showed no significant antibacterial effects in vitro against various bacteria, even at high concentrations. Oral doses up to 6 g in humans and 0.12-24 g/kg in rats had no ex vivo antibacterial effects[39]. However, an aqueous extract showed notable antibacterial activity attributed to andrographolides and arabinogalactan proteins[40]. Similar outcomes were seen with crude aqueous leaf extract against gram-positive bacteria but not *E. coli* or *K. pneumoniae*[41]. *Andrographolide*, *neoandrographolide*, and 14-deoxy-11,12-didehydroandrographolide exhibited viricidal effects against herpes simplex virus 1 (HSV-1) without cytotoxicity at effective concentrations[43].

The alcohol extract of the rhizome displayed significant in vitro activity against *Ascaris lumbricoides*[44]. The chloroform extract completely inhibited malarial parasite growth within 24 hours at 0.05 mg/mL, and methanol extract showed similar inhibition within 48 hours at 2.5 mg/mL[45]. Methanol extract also significantly inhibited *Plasmodium falciparum* with an IC₅₀ of 7.2 µg/mL[46]. Xanthones from the plant's roots exhibited in vivo and in vitro anti-malarial activity against *Plasmodium berghei* and *Plasmodium falciparum*[47]. These xanthones also showed antiprotozoal activity against *Trypanosoma brucei*, *Trypanosoma cruzi*, and *Leishmania infantum*[48]. Water decoction of the leaves exhibited filaricidal activity in vitro and in dogs[49]. However, clinical relevance is uncertain due to in vitro/ex vivo studies with potentially non-feasible concentrations.

Cardiovascular Effects

The aqueous extract of *Andrographis paniculata* reduced systolic blood pressure in hypertensive and normotensive rats, linked to ACE activity reduction and kidney lipid peroxidation in hypertensive rats[50]. The hypotensive effects of n-butanol and aqueous fractions were influenced by certain agents[51]. 14-deoxy-11,12-didehydroandrographolide (DDA) reduced blood pressure and heart rate in rats, affected by propranolol, hexamethonium, and captopril[52]. DDA demonstrated hypotensive and negative chronotropic effects through vascular smooth muscle action[53].

A. paniculata's effects on experimental myocardial infarction were explored. In dogs, the extract restricted infarct size and ultrastructural changes[54][55]. Post-ischemia extract administration maintained cardiac output and rhythm, preventing ventricle end-diastolic pressure increase[58]. Andrographolide protected rat cardiomyocytes from hypoxia/reoxygenation injury, raising glutathione levels and antioxidant enzyme activities[59].

In rabbits, the extract prevented atherosclerotic stenosis and hindered restenosis post-angioplasty[60][61]. Aqueous extract, andrographolide, and DDA inhibited platelet aggregation in various ways[62]. *A. paniculata* extract reduced platelet aggregation and serotonin release in patients[63].

While evidence supports hypotensive and cardiovascular effects, more research is needed on mechanisms, constituents' roles, interactions, and clinical efficacy. Further investigation is required to comprehend cardiovascular and platelet effects in clinical scenarios.

Antioxidant and Anti-inflammatory Activities

Researchers have highlighted *Andrographis paniculata*'s antioxidant and anti-inflammatory properties. Water and ethanol extracts, along with andrographolide, prevented nicotine-induced mitochondrial electron chain complex inhibition, curbing nitric oxide (NO) increase in rat brain regions[64][65]. Aqueous extract enhanced liver defense enzymes and reduced lactate dehydrogenase activity in lymphoma-bearing mice[66]. Methanol extract inhibited reactive oxygen species (ROS) formation and suppressed carrageenan-induced inflammation[67]. Andrographolide reduced ROS accumulation induced by phorbol-12-myristate-13-acetate (PMA) and neutrophil adhesion caused by N-formyl-methionyl-leucyl-phenylalanine (fMLP)[68][69].

Inflammation involves excessive NO and prostaglandin E₂ (PGE₂) levels from iNOS and COX-2 expression in activated macrophages. Methanol extract, andrographolide, and neoandrographolide inhibited LPS-stimulated NO production, possibly via reduced iNOS expression[70-73]. Andrographolide restored aorta response after LPS incubation and mitigated blood pressure decline in rats due to LPS[71]. Neoandrographolide suppressed NO production ex vivo after oral administration[69]. Andrographolide inhibited TNF- α and granulocyte-macrophage colony-stimulating factor induced by LPS[74]. Neoandrographolide hindered PGE₂ synthesis, TNF- α , and reduced edema and vascular permeability in mice[75]. A refined *A. paniculata* extract reduced lipid peroxide, and endothelin, and enhanced NO, cGMP, and superoxide dismutase activities in

atherosclerotic rabbits[76].

Antihyperglycemic and Hypoglycemic Effects

A. paniculata extracts and andrographolide exhibit antihyperglycemic effects. The water extract effectively counters glucose-induced hyperglycemia in nondiabetic rabbits, with no impact on epinephrine-induced hyperglycemia or fasting blood glucose levels[77]. Ethanol extract reduces fasting serum glucose in diabetic rats, elevating body weight, and enhancing antioxidant enzyme activities[78]. An ethanol extract significantly reduces fasting serum triglycerides in diabetic rats more than metformin[79]. Aqueous extract decreases blood glucose levels in streptozotocin-diabetic rats, with freeze-dried material showing pronounced effects[80]. Oral administration of *A. paniculata* leaves reduces blood glucose levels, increases antioxidant activity, and curbs food and water intake in diabetic animals[81]. Andrographolide reduces plasma glucose concentration dose-dependently in diabetic and normal rats, possibly by enhancing glucose utilization and insulin release[83][84]. Both extracts and andrographolide may inhibit alpha-glucosidase and alpha-amylase enzymes, contributing to hypoglycemic effects[85]. The extracts and andrographolide may employ distinct mechanisms for hypoglycemic effects in different contexts. The water extract's limited effect on fasting blood glucose in nondiabetic animals could warrant further exploration to uncover potential blood glucose-lowering constituents[77][81].

Effects on Reproductive Systems

A. paniculata's effects on reproductive systems are conflicting. In male Wistar mice, powdered stem administration displayed antifertility effects, while fertility remained unaffected in females[86,87]. Administration of aerial parts decoction induced abortion and prevented implantation in female albino mice, possibly involving interference with progesterone activity[6]. Female mice fed sun-dried *Andrographis* powder exhibited pregnancy inhibition[88]. In male albino rats, *A. paniculata* leaf powder inhibited spermatogenesis, while andrographolide administration to male rats reduced sperm count and motility[89][90]. However, other studies reported no testicular toxicity in rats exposed to *A. paniculata* extract[91]. *A. paniculata* extract did not affect progesterone levels in pregnant rats and induced uterine relaxation by inhibiting calcium channels[92][93]. A clinical study showed no significant impact on sperm quality and fertility in healthy adult males[94]. Inconsistencies exist, making it challenging to draw definitive conclusions, but *A. paniculata's* effectiveness as birth control seems unlikely. Further research into short- and long-term fertility effects is necessary.

Conclusions and Other Potential Uses

A. paniculata's consistent hepatoprotective effects and its inclusion in polyherbal formulations for liver ailments emphasize its potential, though further investigation is needed. Variability in antibacterial effects might arise from diverse factors, including constituent variations due to collection and extraction methods. *A. paniculata's* impact on blood pressure, cardiovascular conditions, and platelet aggregation is promising but requires comprehensive clinical research. Antihyperglycemic activity is evident in diabetic rats, driven by mechanisms like enhanced antioxidant activity, improved glucose utilization, and insulin release, which merit further study. The evidence supports *A. paniculata's* potential for treating URTIs and self-limited infections.

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