

GREEN CHIRETTA (*Andrographis paniculata*. L): AN INDIGENOUS HERB OF INDIA WITH POTENTIAL HEALTH BENEFITS

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Abstract

Green chiretta (*Andrographis paniculata*. L), is a plant that belongs to the family Acanthaceae and is a native to the Indian subcontinent. It is a splendid medicinal plant that is used universally in traditional medical systems for curing multiple ailments. It contains an array of phytochemicals like diterpenes, lactones, paniculides, polyphenols, noriridoides, xanthenes, and flavonoids which makes it a miracle medicine. The review article sheds light on the therapeutic benefits of various extracts/fractions of *Andrographis paniculata*. A systematized search of the available literature was performed using databases from Google Scholar, PubMed, Elsevier, Wiley, Web of Science, and ResearchGate using a combination of various relevant keywords. Scientific evidence strongly declares that andrographolide is the active major component that is responsible for a broad spectrum of pharmacological properties of this plant. Andrographolide is present in all parts of the plant including the root. Infusions of *A. paniculata* is widely used as a treatment for fevers in the traditional system of medicine and could be extremely beneficial owing to its proposed antiviral activity. An in-depth study on the properties of *A. paniculata* will help out the scientist population in finding out a drug without any adverse effects for treating the current pandemic.

Keywords: Andrographis, Andrographolide, Malaria, SARS, COVID -19.

Introduction

A. paniculata, is an annual, branched, erect herb. It belongs to the family of Acanthaceae and mostly grows in parts of South East Asia, and America. ^[1] This crop is widely grown in South-eastern Asia, for curing bacterial infections and some degenerative diseases. ^[2] The leaves are used as salad with other vegetables and as an infusion for fever in Indonesia.^[3]

A. paniculata has been used to treat a variety of illnesses, including inflammation, allergic reactions, and an immunomodulator. Several investigators have confirmed the anti-inflammatory effects of *A. paniculata* and its bioactive components.

It produces small pink flowers which are solitary and arranged in lax spreading racemes or panicles. Its fruits are capsules about 2 cm in length.^[4] It has several yellow-brown seeds which may be subquadrate, rugose, and glabrous. It produces flowers from September to December ^[5] *Paniculata* is used in the traditional medical system throughout the world as a dietary supplement for healthy well-being. ^[6] In India, *A. paniculata* is used as a cure for liver diseases.^[7]

A. paniculata is used as a remedy for upper respiratory tract infections. Parts of the herb are consumed as an infusion, or powder, either alone or in combination with other medicinal plants. [8]

Therefore, the objectives of this review is to : (i) to analyze the properties of phytochemicals present in it (ii) to scrutinize the therapeutic properties of *Andrographis paniculata* through a thorough study of the review of literature

Literature Search

Online search was conducted through several databases including PubMed, Elsevier, Google Scholar, Research gate, MDPI, and Springer. Scientific publications between 2015 to 2021 that contained terms such as “andrographolide and its derivatives”, “*Andrographis paniculata*”, “antiviral activities”, “mechanism of action”, “Phytochemicals” in their titles and abstracts were shortlisted. Studies that gave positive results in both invitro and invivo studies were selected for the review. The search generated about one hundred research publications among which 75 publications were selected.

Common names

A. paniculata is generally known as Indian *Echinacea*. [9] In India, it has various regional names such as *Mahatikta* (Sanskrit), *Kiryato* (Gujarati), *Mahatita* (Hindi), *Kalmegh* (Bengali). (Table 2). The gamut of factors such as geographical region, harvest time, and processing method alters the phytochemical content of the plant. [10]

Phytoconstituents

Various metabolites including paniculides, farnesols, noriridoides, xanthenes, polyphenols, and trace elements have been isolated from the plant parts. [11] The whole plant of *A. paniculata* possesses diterpenes, lactones, flavonoids and diterpenoids in *A. paniculata* have curative properties. [12] These compounds are more intense in the leaves of *A. paniculata* when compared to stem, fruit, and root. Thorough Phytochemical assessments scientifically proved that the leaves were comprised of two bitter principles, andrographolide, and kalmeghin. [13] Apart from the above-mentioned compounds another four lactones – A (deoxyandrographolide), B (andrographolide), C (neoandrographolide), and D (14-deoxy-11, 12-didehydroandrographolide) were discovered from the aerial parts. [14]

Therapeutic benefits

Andrographis paniculata as a cure for various viral infections

Anti-dengue activity

Andrographolide targets C6/C3 cell line, HepG2, and HeLa cells inhibit 97.23% of the virus using 15.62 µg/mL. The compound is found to reduce septicity and inhibit the synthesis of the virus with EC₅₀ values of 21.304 and 22.739 µM, respectively. [15]

Anti-influenza

Andrographolide, 14-Deoxy-11,12-didehydroandrographolide acts on the human bronchial epithelial cell line and decreased the viral action with IC₅₀ values of 5 ± 1 and 38 ± 1 $\mu\text{g/mL}$, respectively. [16] Andrographolide, 14-Deoxy-11,12-didehydroandrographolide targets human T cell, HL2/3 cell, MT2 cell and obstructs the p24 antigen with an EC₅₀ value of 56.8 $\mu\text{g/mL}$. [17]

Effect on Common Cold

Dried leaf powder of *Andrographis paniculata* for five days was given to sixty-one adults ailing from common. Tremendous response to 1200 mg powder was found on the fourth day itself. Strong analgesic activity was detected when andrographolide was taken by mouth in a dose of 300 mg/kg daily. [18]

The results proven (on 223 patients) by KalmCold™ made from andrographolide was twice better than placebo (p -value ≤ 0.05) in controlling the respiratory infections. [23] In a similar trial conducted by Kan Jang on 59 patients exhibited better efficacy of *A. paniculata* extracts than a placebo in trimming down clinical symptoms of common cold. Numerous trials signifies that *A. paniculata* has a high market value, either in the form of its parts or standard compounds. [19]

In vitro antimalarial activity

Evaluation of in vitro anti-malarial activity was assessed using plant extracts against various strain of *P. falciparum*. The malaria SYBR Green I-based fluorescence assay was carried out for evaluating the 50% inhibitory concentration (IC₅₀) of the extracts tested. The highest concentration of test samples was 50 $\mu\text{g/ml}$ [25] (Huang et al., 2020). Data were analyzed to obtain inhibitory concentration (IC₅₀) values for plant extracts. Inhibition concentration was above 10.0 $\mu\text{g/ml}$ and demonstrated powerful antiparasitic activity. [20]

Anti-SARS activity

Andrographolide controls the viral activity by establishing resistance to the entry of the virus, prohibiting gene replication and the secretion of functional proteins by the virus. [21]

Andrographolide is believed *in silico* to have anti-SARS-CoV-2 activity through a precise attack of the host ACE2 receptor and viral enzymes and spike protein. An enzyme-based assay and a phenotypic cell-based immunofluorescent assay (IFA) were carried out to prove the repressive effect on SARS-CoV-2 in African green monkey kidney cells. [22]

A plaque assay was carried out with human lung epithelial cells, Calu-3, was done to ascertain the anti-SARS CoV-2 activity of, andrographolide. SARS-CoV-2 at 25TC ID50 was able to reach the maximal infectivity of 95% in Calu-3 cells. Post-infection treatment in

SARS-CoV-2-infected Calu-3 cells significantly inhibited the production of infectious virions with an IC₅₀ of 0.036 µg/mL and 0.034 µM, respectively. [23]

Aforesaid investigation results give favorable results that *A. paniculata* and andrographolide can be used in the treatment either singly or in combination with added medicines to cure SARS-CoV-2 infection [24]

Antiviral Effect against herpes simplex virus.

Andrographolide and its derivatives is reported to have potent anti-viral activity against a diverse group of viruses belonging to different families including influenza A virus (H1N1), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Herpes simplex virus 1 (HSV-1), Chikungunya virus (CHV), Human immunodeficiency virus (HIV), Human papillomavirus (HPV) and Epstein-Barr virus (EBV) that belongs to the various viral family such as Orthomyxoviridae, Hepadnaviridae, Flaviviridae, Herpesviridae, Togaviridae, Retroviridae, Papillomaviridae, and Herpesviridae, respectively. [25] Monoester of dehydroandrographolide possesses anti-HIV activity by hindering the pairing of HIV to host cells, reducing the copy number of HIV RNA, dysregulating the signalling pathways in cells, and increasing the T-lymphocytes in HIV-infected individuals. [26]

Anti-Inflammatory Effect

The active component, andrographolide demonstrated anti-inflammatory effects through downregulation of the proinflammatory cytokines-mediated expression of adhesion molecules and leucocyte-endothelial cell adhesion. [27] A study by Iruretagoyena et al. states that demyelinating disease of the central nervous system, autoimmune encephalitis can be treated by daily ingestion of andrographolide at a dose of 4 mg/kg. The balance between proinflammatory and anti-inflammatory cytokines is due to andrographolide. [28]

Antidiabetic activity

A. paniculata extracts and andrographolide effectively showed hypoglycemic effect by

- (a) attenuating plasma glucose level by controlling the level of enzymes α -glycosidase and α -amylase
- (b) enhancing glucose uptake and oxidation by peripheral tissues
- (c) modulating the lipid storage in cells. [29]

Reduction of fasting blood glucose (FBG), increased level of insulin, suppressed the effect of triglycerides (TG), and low-density lipoproteins (LDL) along with various other favorable outcomes in streptozotocin (STZ)-induced diabetic rats were observed. [30] Administration of the purified extract of *Andrographis paniculata* for 5 days significantly decreased ($P < 0.05$) preprandial and postprandial blood glucose levels in high-fat-fructose-fed rats in a dose-dependent manner. At doses of 434.6 and 1303.8 mg/kg b.wt twice daily the extract decreased the preprandial blood glucose level by $41.12 \pm 7.50\%$ and $45.76 \pm 9.89\%$, respectively. The extract also decreased the postprandial blood glucose level by $53.55 \pm 13.75\%$ and $60.14 \pm 12.39\%$, respectively. [31]

Cardiovascular Effect.

Andrographis paniculata is used as an adjunct therapy for heart health in traditional medicinal systems. Wang et al. reported that AP has the potential to increase the nitric oxide, cyclic guanosine monophosphate, and superoxide dismutase activity with declines of lipid peroxide and endothelin in an atherosclerotic rabbit model. [32]

Wang and Zhao proved that the *Andrographis paniculata* extracts inhibit narrowing of arteries and improve blood clotting time in the pre-and postangioplasty trials. The extracts inhibited cell growth and DNA synthesis in a dose-dependent manner, which is a similar mechanism to stents that prevent cell division. [33] Andrographolide ameliorates adipogenesis during the transformation of 3T3-L1 pre-adipocytes to mature adipocytes in rats. [34] (Shi et al., 2020) In addition to downregulating the expressions of sterol regulatory element-binding protein (SREBP), and decreased cellular lipid accumulation, andrographolide has been shown to ameliorate the body weight gain in mice as well as fat content in the liver, adipose tissues, blood, with a cumulative result of improvement in insulin and glucose sensitivity. [35]

Hypotensive effect

The hypotensive effect could be related to the action of the andrographolide derivative, 14-deoxy-11,12-didehydroandrographolide on vascular smooth muscle cells. [36] Components other than andrographolide through diverse mechanisms are also suggested for the hypotensive effect of the plant extract. Another effect relevant to metabolic syndrome is inhibition of platelet aggregation by andrographolide. [37]

Hepatoprotective Effect.

A. paniculata is widely used traditionally as a hepatoprotective tonic to stimulate the secretion of multiple enzymes. [38] In a comparative study, the leaf extract and andrographolide were tested against the carbon tetrachloride- (CCl₄-) induced hepatic microsomal lipid peroxidation. Only the leaf extract completely protected the high concentration CCl₄-induced microsomal lipid peroxidation in vitro but not the andrographolide, which indicated that the hepato-protective role is not solely due to the presence of andrographolide. [39]

Antibiotic Effect.

Dichloromethane, methanol, and aqueous extract of *paniculata* was tested for treatment against skin infection. Zone of inhibition was observed against all the tested bacterial strains in different concentrations. Methanol extract showed the highest antibacterial activity against *Enterococcus faecalis* at 1000 µg/disc with an inhibition zone of 24 mm, and dichloromethane extract showed the least activity against *Neisseria meningitidis* at 250 µg/disc with an inhibition zone of 6 mm. [40] Study by Sule et al., 2019 [41] proved antibiotic activity of *Andrographis Paniculata* against pathogenic bacteria such as *S. aureus*, *Streptococcus pyogenes*, *Micrococcus luteus*, *Proteus mirabilis*, and *P. aeruginosa*. Their results revealed that the highest inhibition (19.67 ± 0.76 mm) was exerted against *S. aureus* at 1000 µg/mL and the least (07.00 ± 1.50 mm) activity shown against *P. aeruginosae* at 250 µg/mL. [42]

Anticancer Effect.

Ethanollic fractions caused apoptosis in skin cancer cell lines and the cell become isolated from the other cells by shrivelling and diminution. Dichloromethane fraction of andrographolide significantly inhibited the proliferation of HT-29 colon cancer cells. In contrast, recently Aditya et al. reported that methanol extract of *Andrographis paniculata* was not active against breast and colon cancer cell lines. The meagre response observed may potentially be due to poor absorption of the biocomponent. [43]

Immunomodulatory Effect.

AP is known to exert several immunomodulatory properties. Lab tests have demonstrated that *Andrographis paniculata* inhibited the growth of human breast cancer cells similar to the drug tamoxifen. [44] Fong et al. 2012 reported that andrographolide improved the functioning of immune system by accelerating antibody secretion and phagocytosis. [45]

Antihyperuricemic effect

Anti-gout effect of *A. paniculata* leaf extracts was confirmed by exploring the xanthine oxidase (XO) inhibitory assay on rats. The baseline serum uric acid levels were from 1.59 to 1.68 mg/dl and after 14 days of supplementation, serum uric acid levels ($p < 0.05$) decreased to 2.59, 2.54, and 2.48 mg/dl, respectively, compared to control group. [46]

Sexual Functions and Contraceptive Effect.

Andrographis paniculata and andrographolide showed either contraceptive or fertility on a dose dependent manner. *Andrographis paniculata* exhibited contraceptive effects by ceasing the formation of sperms in male albino rats [47–51]. Joseph et al., 2020 reported female mice that were fed *Andrographis* became sterile and did not conceive even after mating with male of potential fertility proving the contraceptive effect. [52,53] The antifertility effects of andrographolide are characterized by distinct decline in the level of specific amino acids, substantial increase in lipid, sugar and liver enzymes level in the body of mice. [54]

Safety and Toxicity Effects.

Consumption of *Andrographis* orally causes vomiting due to its bitter taste. Some adverse effects including allergic reaction, tiredness, myalgia, dysphagia, watery stools, and dysgeusia. [55] Expecting women are advised not to consume the extract as it is detrimental to the growth of fetus [56,57]

Generally, uses of *Andrographis paniculata* as a medicine have been proved to be safe in various studies on rodents and in supplementation studies.. Few studies showed the toxic effect of *Andrographis paniculata* on male genital system by affecting the sperm cells. [58]

Conclusion

The prevailing pandemic presses the need for *Andrographis paniculata* due to its myriad of healing property. More light could be thrown on the research of *Andrographis paniculate*

against hyperglycemia, antitumour and reteroviral activities, on human subjects would bring a lot of benefits for the globe. As the world is grappling with COVID 19, an alternative medicine like *Andrographis paniculata* would be of great use to the humankind. Owing to its low bioavailability and absorptive power, Andrographolide is yet to reach its full therapeutic potential. Effective mode of drug delivery system is the need of the hour to heighten its bioavailability. Further high-quality studies, supplementation trials with large population size are needed to strongly establish the clinical effectiveness of the bioactive components of *Andrographis panniculata*.

The author does not have a conflict of interest.

Short name: Andrographis, a potent drug for viral infections.

Table 1: Morphology of *Andrographis paniculata*

| Traits | Characteristics |
|-------------------------|--|
| <i>Plant height</i> | <i>30 -110 cm</i> |
| <i>Stem – Colour</i> | <i>Dark green</i> |
| <i>Length</i> | <i>30 -100</i> |
| <i>Diameter</i> | <i>2- 6</i> |
| <i>Shape</i> | <i>Quadrangular, slightly enlarged at the nodes.</i> |
| <i>Leaves – Length</i> | <i>2 -12 cm</i> |
| <i>Width</i> | <i>1 -3 cm</i> |
| <i>Shape</i> | <i>Glabrous</i> |
| <i>Flowers – Colour</i> | <i>White with purple spots</i> |
| <i>Size</i> | <i>Small</i> |
| <i>Seed – Shape</i> | <i>Capsules, linear oblong at both ends</i> |
| <i>Size</i> | <i>1.9 X.3 cm</i> |
| <i>Colour</i> | <i>Yellowish brown</i> |

Table 2: The vernacular names of *A. paniculata* in various countries

| Countries | Vernacular name |
|------------------|-----------------------------|
| Myanmar | Segagy |
| China | Chuan Xin Lian and Kan Jang |
| Thailand | <i>Fah Talai Jone</i> |
| French | Chirette Verte |
| Indonesian | Sambirotto |
| Urdu | Kalmegh |
| Spanish | Andrographis |
| Japan | Shenshinren |
| Persian | Nain e havendi |
| Malay | Hempedu |
| Philippines | Lekha |
| Scandinavia | Green chiratta |
| Russian | Andrografis |

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