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REVIEW ARTICLE

Experimental and Clinical Evidence of *Andrographis paniculata* (Roxb.) Wall. Ex Nees (Bhunimba) - A Review

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ABSTRACT

The plant *Andrographis paniculata* is a drug identified as a source plant of Bhunimba often referred as Kalamegha or Yavatikta mentioned in Ayurvedic literature. Bhunimba is indicated in Kushta (skin diseases), Kandu (itching), Shopha (swelling), Yakratroga (liver diseases), Krimi (worm's infestation), Kushta (skin diseases), Jwara (fever). This drug having chemical constituents like Andrographolide, 14 – deoxy – 11, 12 – didehydroandrographolide etc., in it. *A. paniculata* is reported to have hepatoprotective, antiulcer, anti-inflammatory, antipyretic, anti-filarial activities etc. Clinically also it has shown significant result in viral hepatitis, elephantiasis, common cold, vitiligo and upper respiratory tract infection.

Key words: Bhunimba, Andrographolide, 14 – deoxy – 11, 12 – didehydroandrographolide.

INTRODUCTION

Man has used plants and plant parts for medicinal purposes from time immemorial. The ancient scriptures of all civilizations are replete with innumerable references of medicinal plants. In fact, there is no plant under the sun, which arguably does not have any medicinal properties. Medicinal plants play an important role in various traditional systems of medicines of different countries such as Indian Systems of Medicines (Ayurveda), Traditional Chinese Medicines, Tibettian Medicines, etc. Around 40% or more of the pharmaceuticals of the world are using certain plant extracts or active principles derived from natural resources. The researchers are interested towards the plants, hitherto unexploited or under exploited, for medicinal purposes [1].

In Ayurvedic classics less importance was given for the identification plants, because in those days humans were closer to the nature and they easily identified the drugs grows in the nature. Now a day people are living away from the nature resulting in lack of compression to identify the drugs. On other hand common synonyms mentioned for different drugs also created confusion in establishing identification of drugs. *Andrographis paniculata* is popularly known as Bhunimba in M.P. and Nagpur area and as Cirayata in the Bihar. Kalamegha is another common name given to this plant. It has also been identified with Yavatikta of the texts. All these facts lend scope at the possibility of *Andrographis paniculata* being Bhunimba of the texts with Yavatikta as its synonyms [2].

The analysis was carried out based on the collected information from various sources including review articles; Ayurvedic classical texts & lexicons; Ayurvedic pharmacopoeia of India as well as many other reference books.

PROPERTIES (GUNA) AND ACTIONS (KARMA):

Rasa (taste): Tikta (bitter)
Guana (quality): Laghu (light), Ruksha (dry)
Virya (potency): Ushna (hot)
Karma(action): Kaphapittahara, Jwarahara (antipyretic), Vranasamropana (wound healing), Deepana

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(increases digestive power), Swedana (fomentation), Krimighna (worms) [3, 14].

INDICATION DESCRIBED IN AYURVEDIC MEDICINE:

Kushta (skin diseases), Kandu (itching), Shopha (swelling), Yakrutroga (liver diseases), Krimi (worms), Jwara (fever) [3].

USES DESCRIBED IN FOLK MEDICINE:

Actions [4]**:**

- Whole plant: stomachic, blood purifier, liver tonic, anti-dysenteric, anti pyretic, anthelmintic, wormicidal, anti-malarial, anti-diabetic and febrifuge.
- Leaves: febrifuge, stomachic, anthelmintic, aphrodisiac and liver tonic.

Indications [4]**:**

- Whole plant – snake bite, scorpion sting, centipede sting, jaundice, fever, anemia, scabies, infective hepatitis, dyspepsia, skin diseases, leucoderma, eczema and wounds.
- Seeds- diarrhea.
- Leaves - scabies, snake bite, scorpion sting, skin diseases, eczema, lung diseases, constipation, malaria, cholera, tumor, abdominal pains, flatulence, dysentery and dyspepsia.
- Root - poisonous bites, rheumatic pains, liver disorders, fever, whooping cough, intestinal worms and stomach ache.

FORMULATION IN AYURVEDIC CLASSICS:

Bhunimbadi churna [5], Asthapanayoga [6], Katukadya ghrita [7], Mahatiktaka ghrita [8], Patoladi ghrita [9], Pittapachaka kwatha [10], Panchagavya ghrita [11], Rodhrasava [12], Aragvadhadi kwatha churna [13], Nimbadi kwatha churna [14], Panchamrita kwatha churna [15], Bharngyadi kwatha churna [16], Vasaguduchyadi kwatha churna [17], Tiktaka ghrita [18], Patoladi ghrita [19], Maha panchagavya ghrita[20], Chandraprabha vati [21], Dhanvantara gutika [22], Manasamitra vataka [23].

CHEMICAL CONSTITUENTS:

- Major – 0.5 – 0.9% andrographolide, a diterpene lactone.
  Minor – include diterpene lactones viz, andrograpanin, deoxyoxoandrographolide. Glycosides viz, neoandrographolide and andrographiside. Flavonols viz, oroxylin, wogonin, andrographidines A, B, C, D, E and F [24].
- **Whole plant** - gave the following - lactones (dry basis): andrographolide, 0.6, 14-deoxy-11-oxo-andro-grapholide [$C_{20}H_{28}O_5$, mp 98-100˚), 0-12; 14 – deoxy – 11, 12 – didehydroandrographolide [$C_{20}H_{30}O_4$, mp 203-04˚), 0,06, 14-deoxyandrographolide [$C_{20}H_{30}O_4$, mp 175˚), 0.02%, and a non bitter constituent, neoandrographolide [$C_{26}H_{40}O_8$, mp 167-168˚] , 0.005 % [25].
- **Leaves** - contain andrographolide (yield, 1%), petroleum ether extract of the leaves has shown α-β-unsaturated lactone, homoandrographalide [$C_{22}H_{32}O3$, mp 115˚], andrographosterol [$C_{23}H_{38}O$, mp 135˚], andrographane [$C_{40}H_{82}$, mp 67-68˚], andrographone [$C_{32}H_{64}O$, mp 85˚], two esters containing hydroxyl groups [25].
- **Roots** - apigenin-7, 4-di-o-methyl ether, andrographolide and a new natural flavone, 5-hydroxy 7, 8, 2, 3-tetra methoxyflavone [$C_{19}H_{18}O_7$, mp 150-51˚, yield 0.006%]]. They also contain a monohydroxytrimethyflavone,andrographin $C_{18}H_{16}O_6$, mp 190-91˚ and a dihyroxy-di-methoxyflavone, panicalin[$C_{17}H_{14}O_6$, mp 263-64˚]. Presence of α-sistosterol is also reported [25].

EXPERIMENTAL PHARMACOLOGY:

Hepatoprotective:

1) Oral administration of aqueous extract of the leaves to mice delayed the hepatic tumourgenic condition induced by hexachlorocyclohexane. Hepatoprotective activity of the extract was confirmed and suggested to be due to antioxidant action [4].
2) A single dose of andrographalide and "Kalamegha" leaf extract (500mg/kg orally) prevented CCl4 induced changes in enzyme activities in serum and liver of rats [4].
3) The crude aqueous extract (2%) of the plant showed inactivation of HBsAg positive serum samples in *invitro* studies in 48-120h at 37 degree C [4].
4) Alcoholic extract of the leaves obtained from the cold maceration at a dose of 300 mg/kg administered orally to albino rats

showed hepatoprotective activity against CCl4 induced liver damage [4].

5) Andrographolide in a dose of 20-80 mg/kg exhibited a strong choleratic action when administered i.p. to albino rats [4].
6) Andrographolide showed a significant dose dependent protective activity against paracetamol induced toxicity on ex-vivo preparations of isolated rat hepatocytes [4].
7) Alcoholic extract of the fresh plant and two of its constituent diterpenes, andrographolide and neoandrographolide showed significant anti-hepatotoxic action in plasmodium berghei K173 induced hepatic damage in mastomys natalensis [4].

Anti ulcer:

Apigenin 7, 4-di-o-methyl ether the flavones isolated from the root showed a significant dose dependent antiulcer activity in Shay rats, histamine induced ulcer in guinea pigs and in aspirin induced ulcer in rats [4].

Anti inflammatory:

1) Aqueous extract of the plant at a dose 20mg/kg given orally in rats inhibited carrageenin induced oedema after 3 hrs as compared to the control rats [4].
2) Andrographolide has shown a mild anti inflammatory activity compared with corticosteroids and conventionally used NSAID [26].

Effects on C.N.S:

Andrographolide is known to cross the blood brain barrier and concentrates in the brain and spinal cord. It may act as the Barbital receptors in the brain [26].

Antipyretic:

Andrographolide in a dose of 100-300mg/kg produces significant antipyretic activity [26].

Antifilarial activity:

1) The water decoction of the leaves was tested both in vitro and in vivo against canine filariasis. The decoction killed *invitro* the microfilarae dipetalonema reconditum in 40 min [4].
2) Aqueous extract of dried leaves has *(invitro)* anti filarial action [27].

Analgesic:

Andrographolide shows significant analgesic activity in acetic acid writhing in mice and ran dull selitters test in rat at 300mg/kg dose [26].

Cardiovascular system:

1) *Andrographis paniculata* given to dogs one hour after development of myocardial infarction decreased the damage that occurred to the heart muscles. Abnormal E.C.G readings are prevented. It also has anti-platelets aggregation property and fibrinolisis initiating property, which helps to dissolve clots after myocardial infarction [26].
2) *Andrographis paniculata* extract has antihypertensive property is due to the relaxation of smooth muscles in the wall of blood vessels [26].

Anti-diarrheal:

The alcoholic extract plant exhibited significant anti-diarrheal activity against Escherichia coli enterotoxins in animal models [4].

Anti-malarial:

1. The alcoholic extract of the plant was found to possess schizontocidal activity in vivo as well as in vitro at a dose of 1 g/kg 4d and 100mg/ml, respectively against the NK 65 strain of Plasmodium berghei in mastomys natalensis [4].
2. Chloroform extract of this plant has shown (i*n vitro & in vivo)* anti-malarial activity [27].

Antibacterial and Antifungal:

1. Alcoholic and aqueous extracts of the leaves showed antibacterial activity against staphylococcus aureus and Escherichia coli [4].
2. Extracts of the shoots showed antimicrobial activity against Escherichia coli and Staphylococcus aureus [4].
3. 80% ethanolic extract of the root using Agar diffusion method revealed antibacterial activity against a strain of Escherichia coli and pseudomonas aeruginosa at a conc. Of 25mg/ml and also active against Bacillus sutilis and Staphylococcus aureus in conc. Of 6.25 and 12.5 mg/ml respectively [4].
4. Alcoholic extract of the plant at a conc. 200mg/ml showed antibacterial activity against staphylococcus aureus, bacillus subtilis, escherichia coli and pseudomonas aeruginosa devoid of action against slmonella typhimurium and proteus vulgaris [4].

5. Plant extract revealed antifungal activity against Helminthosporium sativum and inhibited the mycelia growth of the Keratinophilic fungi Microsporum gypseum, Chrysosporium tropicum and Trichophyton terrestre in *in vitro* studies [4].
6. The alcoholic extract and aqueous extract against Aspergillus niger at conc. Of 5 and 2.5 % [4].

Anthelmintic:

1) Aqueous extract of the plant showed nematicidal activity against the root knotnematode meloidogyne incognita on tomato both *in vitro* and in pot [4].
2) Alcoholic extract shows a good anthelmintic activity against human Ascaris lumbricoides (Intestinal round worm) [27].
3) The crude extract of the leaves revealed 100% mortality of soil nematodes within 12h of treatment. The other parts of the plant also had same activity [4].

Anti-cancer:

Methanolic extract of the herb showed significant Anti cancer activity in anti-cellogram essay *(in vitro)* [27].

Anti atherosclerotic activity:

Animal experiments have shown anti atherosclerotic activity and it has been suggested that this plant preparations may help in preventing re-stenosis of arteries after coronary angioplasty [27].

General activities:

Effect of alcoholic extract of the plant on the cobra venom induced death in mice was studied. The extract prolonged the life time of venom injected animals as compared to the controls [4].

PHARMACOKINETIC PROPERTIES:

According to recent research, andrographolides are highly bioavailable in humans. Following oral administration, doses of 20 mg of andrographolides are readily absorbed, reach a peak plasma value in 1.5-2 hours and have a mean plasma residence time of 10 hours (Panossian *et al* 2000). Labeled andrographolide is readily distributed throughout the body, including brain and spinal cord. After 72 hours, nearly 90% of andrographolides are excreted, mostly by urinary excretion, although there is still some discussion about this (Wuxi Medicine Institute 1979) [28].

METABOLISM:

A. paniculata has been widely explored using signal transduction technique. Extracts of *A. paniculata* have been found to counter act interference with the cell cycle. Bio distribution experiments done over the experimental animals followed by radioactive labeled andrographolide, the compound appears to be widely distributed in the body. High concentrations are noted in the central nervous system especially in the brain and spinal cord and other organs with high blood flow. Andrographolide appears to have a relative short half-life of approximately 2hrs. andrographolides are excreted rapidly from the body via urine and gastro intestinal tract. In some studies 80% of the administered dose of andrographolide is removed from the body with in 1st 8 hrs with the excretion rate of more than 90% of the compound 48hrs [26].

TOXICOLOGICAL STUDIES:

I. Contraindications:

- The herb is contraindicated in bleeding disorders, hypotension, as well as male and female sterility (exhibited infertility in laboratory animals) [29].
- Pregnancy and lactation
  According to botanical safety handbook, this plant falls in class 2b "herb not to be taken during pregnancy" [2].

II. Undesirable effects:

- Anaphylactic shock (one case) and anaphylactic reactions (two cases) have been reported to the World Health Organization (WHO) collaborating centre for International Drug Monitoring as of June 2003 [30].
- Some people on intake of *A. paniculata* extract experience dizziness and palpitations. Some may develop allergic skin reactions [26].

III. Overdose:

1) Leaves and stem extracts may cause gastric discomfort, vomiting and loss of appetite when given orally in large dose [31].
2) Injection of the crude drug (extract of leaves and stem) extract may lead to anaphylactic shock [31].
3) Andrographolide showed reproductive toxic effects in male albino rats [31].
4) Leaves when fed to male albino rats, andrographolide present in it, causes the arrest of spermatogenesis by preventing

cytokines is of the dividing spermatogenic cells lines [31].

5) As it is called as "King of bitters" it may cause emesis on overdosing. Gastric instability, loss of appetite and nausea are also observed due to overdosing of andrographolide extract [32].
6) Toxicological studies in animal models and in humans confirmed that *A. paniculata* is toxic when given in too high dose. A dose of 10 gm/kg of body weight produces decreased in activities and lethargy. 50mg/kg of dose did not reveal any untoward effects on any of the system [26].

CLINICAL TRIALS:

HIV:

A phase 1 dose-escalating clinical trial of andrographolide from *Andrographis paniculata* was conducted in 13 HIV positive patients and five HIV uninfected, healthy volunteers. No subjects used antiretroviral medications during the trail. The planned regimen was 5mg/kg bodyweight for 3 weeks, escalating to 10mg/kg body weight for 3 weeks, and to 20 kg/kg body weight for a final 3 weeks. A significant rise in the mean CD4 (+) lymphocyte levels of HIV subject occurred after administration of 10 mg/kg andrographolide. There were no statistically significant changes in mean plasmas HIV-1 RNA levels through the trail. Andrographolide has been suggested to inhibit HIV-induced cell cycle dys-regulation, leading to a rise in CD4 (+) lymphocyte levels in HIV-1 infected individuals [31].

Viral hepatitis:

A compound preparation containing *Ocimum sanctum, Tephrosia purpure, Eclipta alba, Andrographis paniculata* and *Terminalia chebula* is claimed to be useful in the management of viral hepatitis. In a clinical trial on 32 patients of viral hepatitis compared to 31 patients on placebo, the course of illness was shortened significantly in drug treated group, the clinical symptoms and the biochemical parameters showing beneficial changes [31].

Slipada (Elephantiasis):

32 cases of Slipada (elephantiasis) were given treatment with Nityanandarasa and Bhunimbavati (single drug preparation of *Andrographis paniculata*) internally and Sarshapalepa prepared with Gomutra (cow's urine) externally. The results of the treatment showed significant reduction of symptoms. It is observed that the response to treatment was good in Kapha dominant cases of Slipada [31].

Common cold:

In placebo-controlled double blind study, the therapeutic effect of KanJang tablet made out of dried extract of *Andrographis paniculata* was tested in patients with common cold. The patients were divided in two group, in which group 1 (33 patients) received 1200mg of *Andrographis paniculata* and group 2 (28 patients) a placebo. A significant reduction in clinical symptoms at day 4 of administration of the KanJanga tablets was observed. KanJanga in a dose of 1200 mg daily has been reported to significantly shorten the course of the disease and is indicated for an enhanced resistance to common cold [31].

Vitiligo:

Andrographis paniculata is one of the constituent of Ayush – 57 an Ayurvedic drug containing the plants *Plumbago rosea, Terminalia belerica, T. chebula, Emblica officinalis* and other constituents, which has been reported to be beneficial in some cases of vitiligo [4].

Anti malignant activity:

Andrographis Paniculata extracts are known to have cytotoxic activity. *A. paniculata* is known to inhibits growth tumors, also inhibits human breast cancer cells similar to the tamoxifen. *A. paniculata* extracts safely and effectively block the growth of prostate cancer and non –Hodgkin's lymphomas. It claimed that probably *A. paniculata* inhibits synthesis of cancer cell DNA [26].

Upper respiratory tract infection:

In Sweden a recent clinical research activity showed significant result of extract *A. paniculata* in the treatment of uncomplicated upper respiratory tract infection. In another clinical investigation (Thailand) efficacy of this herb for the treatment of pharyngotonsillitis in adults has been demonstrated [27].

Labour:

Crude drug has been used clinically to induce labour with effective rate of 89%. The preparation have also been tested (mice, rabbits) for termination of pregnancy, and as an Anti fertility agent [27].

General activities:

Chinese scientists have carried out clinical trials on the efficacy of *A. paniculata*. The crude extracts as well as pure compounds were

evaluated. It was concluded that these preparations are therapeutically effective in case of bacillary dysentery, gastroenteritis, typhoid fever, respiratory tract infection, tuberculosis, pyelonephrities and skin infections [27].

DISSCUSSION

Andrographis paniculata is a plant which is identified as Bhunimba explained in Ayurvedic classics. It is being used as hepatoprotective in modern medical system. In Ayurveda it is indicated in Kushta (skin diseases), Kandu (itching), Shopha (swelling), Yakratroga (liver diseases), Krimi (worms) and Jwara (fever). Andrographolide is a major chemical constituent, which is responsible for the hepatoprotective, anti-inflammatory, antipyretic, analgesic, antihypertensive activities etc., in different animal models. Apigenin 7,4'-di-o-methyl ether the flavones is responsible for the anti ulcer activity. Different extracts of the plant shown significant result in different activities viz., anti-cancer, anthelmintic, antibacterial, antifungal, anti-malarial, anti-diarrheal, anti-filarial, antipyretic and anti inflammatory activities etc., Clinically drug shows significant result in viral hepatitis, elephantiasis, common cold, vitiligo, upper respiratory tract infection and malignant conditions.

Analysis of research data indicates that conditions described for the application of Bhunimba (*Andrographis paniculata*) such Jwara (including Malaria), Switra, Shopha, Krimi and Yakrtroga in Ayurveda are revalidated scientifically.

It occasionally causes dizziness, palpitations and allergic skin reactions. In pregnancy and lactating mothers it is contraindicated. Over dose of leaf extracts shows gastric discomfort, vomiting and loss of appetite.

CONCLUSION

Botanical source of Bhunimba is *A. paniculata*. Andrographolide which is an active principle in the plant which showed significant action in many activities i.e. hepatoprotective, anti ulcer, antipyretic etc., and clinically it also showed significant result in elephantiasis, common cold, vitiligo, upper respiratory tract infection etc., due to its strong potency it creates some undesirable effects and also contraindication in pregnancy and lactating mothers.

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