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Nisha
Govt. P.G. College Syalde Almora, Uttarakhand, India

PB Rao
Department of Biological Sciences, G.B. Pant University of Agriculture and Technology, Pantnagar, U.S. Nagar, Uttarakhand, India

Corresponding Author:
Nisha
Govt. P.G. College Syalde Almora, Uttarakhand, India

Review on pharmacological properties of *Andrographis paniculata* (Burm.f.) Nees

Nisha and PB Rao

Abstract
Andrographis paniculata commonly known as Kalmegh (King of Bitters) belongs to Family Acanthaceae is an important medicinal plant species used in Ayurvedic medicine (prominent in 26 Ayurvedic formulations). The herb possesses astringent properties used to cure bronchitis, cholera, diabetes, influenza, inflammation, itch, piles, gonorrhoea, liver disorder, jaundice and arresting dysentery, blood purifier. Various bioactive compounds such as andrographolide, andrographesterol, andrographopne homo-andrographolide are identified in phytochemical studies which reveal many therapeutic activities. This important plant shows antioxidant, hepatoprotective, antimicrobial, anticancer, antivenom, anti HIV, antimalarial, antipyretic, antifertility, antidiarrhoeal, antidiabetic, antihiperlipidemic activities. Present review have explored the various dimensions of this bitter plant and compiled its vast pharmacological applications to comprehend and synthesize the subject of its potential image of multipurpose medicinal agent.

Keywords: *Andrographis paniculata,* cultivation, pharmacological and medicinal uses

Introduction
Over the past twenty years, interest in medicinal plants has grown enormously from the use of herbal products as natural cosmetics and for self-medication by the general public to the scientific investigations of plants for their biological effects in human beings. Beyond this pharmaceutical approach to plants, there is a wide tendency to utilize herbal products to supplement the diet, mainly with the intention of improving the quality of life and preventing the diseases of elderly people. India has been identified as a major resourceful area in the traditional and alternative medicines globally. *Andrographis paniculata* is well known medicinal plant commonly known as ‘kalmegh’ Kalamegha, meaning "dark cloud". It is also known as Bhui-neem, meaning "neem of the ground", *Andrographis* and Kirayat. It is main herb of the domestic remedy ‘Alui’ which is given to infants from ancient times, in both of the system Ayurveda and Unani. It is advertised in England as a substitute of quinine. This is widely cultivated in Southern Asia, is an herbaceous plant, commonly known as “King of Bitters” belonging to the family of Acanthaceae. It yields not less than 1.0% andrographolide calculated on dry basis. Mostly the leaves and roots have been traditionally used over the countries for different medicinal purpose in Asia and Europe as a folklore remedy for a wide spectrum of ailments or as an herbal supplement for a health promotion. The Indian pharmacopoeia narrates that it is a predominant constituent more than 26 ayurvedic formulation (Gabrielian *et al*. 2002) [22]. In traditional Chinese medicine, it is an important “cold property” herb used to relieve the body of heat, as in fevers and to dispel toxins from the body (Samy *et al*. 2008) [46]. It is commonly used to prevention and treatment of the common cold in Scandinavian countries (Singha *et al*.2003) [51]. *Andrographis* was selected by the ministry of public health as one of the medicinal plants to be included in “the national list of essential drugs A.D. 1999” (list of herbal medicinal products) in Thailand (Mishra *et al*.2009) [37]. Recent research has revealed that *A. paniculata* has a surprisingly broad category of pharmacological activity and some of them are enormously beneficial, such as Anti-inflammatory (Radhika *et al*. 2010, Chao *et al*. 2010) [41, 10, 11] Antidiarrhoel, Antiviral (Calabrese *et al*. 2000) [9], Antimalarial (Iruretagoyena *et al*. 2005) [29] Hepatoprotective (Li *et al*.2007), Cardiovascular (Geethangili *et al*.2008) [23], Anticancer (Niranjan *et al*.2010) [39] and Immunostimulatory activities.

Botanical Description
Herbs to 50 cm tall, annual, much branched. Stems 4-angled, glabrous. Petiole 0.3-1 cm; leaf

blade ovate-lanceolate, lanceolate, or narrowly elliptic, 1.5-7 × 1-2.5 cm, both surfaces glabrous, abaxially pale green, adaxially green, secondary veins 3-5 on each side of midvein, base attenuate and decurrent onto petiole, margin entire, apex acute to shortly acuminate. Inflorescences terminal, leafy panicles of secund racemes; rachis glabrous to sparsely pubescent; bracts triangular to subulate, 1-1.5 mm; bracteoles linear to subulate, 1-1.5 mm. Pedicel 2-9 mm, sparsely pubescent with gland-tipped and non-glandular trichomes (gland-tipped pubescent). Calyx 2.5-3 mm, outside glabrous or gland-tipped pubescent, lobes subulate. Corolla white, 0.9-1.5 cm, outside gland-tipped pubescent; tube basally funnel form for 4-8 mm; lower lip with purple dots, 5-7 mm, erect, lobes ca. 3 mm; upper lip 5-7 mm, reflexed, 2-lobed, lobes ca. 1 mm. Stamens exerted from corolla tube. Style 6-10 mm, sparsely pilose toward base. Capsule ellipsoid-compressed, 1.5-2 × 0.3-0.4 cm, glabrous or sparsely pubescent with gland-tipped trichomes, ca. 12-seeded. Seeds ca. 2 × 1.5 mm, rugose. Fl. and fr. throughout year. 2*n* = 50.

Growth and cultivation

Soil Condition: The plant grows well in all types of soil which explains its wide distribution. It grows in soil types where almost no other plant can be cultivated, particularly 'serpentine soil', which is relatively high in metals such as aluminium, copper and zinc Samantaray *et al*. 2001 [45]. However, soil that is flooded or wet throughout the year may be avoided for its cultivation Kasetklangklung, 1996 [32]. The species was also observed to grow luxuriously in mild humid locations with tropical temperature and high rainfall DMPRD 1990 [20], MPRI 1999 [38].

Cultivation *A. paniculata* prefers sunny condition and is raised from seeds. The seedlings raised in nursery beds should be transplanted to field at a distance of 60 cm × 30 cm with 1 to 3 irrigations during the day periods particularly at flowering stage. In India the seeds of the species are sown in the months of May – June, flowers during August – November and the whole plant starts maturing during February – March. Maximum harvest of total diterpene lactones was noted at blooming from the aerial part.

Harvest: The best harvesting period of *A. paniculata* leaves51 is at 3-5 months old or at 50% blossom whereupon the highest quantity of active lactone compound was found followed by final harvesting after next 2-3 months, with an yield of 2-3 ton per hectare (fresh weight) or 0.5-1 tons per hectare (dried weight).

Post-Harvest and Storage: After harvest, the plants were cleaned and dried (cutting the plant into pieces) in hot air oven at 46°C to 50°C for 8 hours or until properly dried. The dried plant parts were stored in airless plastic bags and kept in clean cool place but not more than a year or otherwise there may be a decrease (up to 25%) in quantity of total diterpene lactone.The stability of andrographolide was determined using a heat-accelerated experiment to reveal a 2nd order kinetics of degradation and the rate constant of decomposition was determined to be 6.58 × 10-6 d -1 at 25°C 53.

Phytochemical constituents

Various chemical constituents in the aerial parts of the *Andrographis paniculata* are andrographolide, which is diterpene lactone, colourless, crystalline, and bitter in taste (Niranjan *et al*. 2010) [39]. Other compounds include 14-deoxy-11-oxoandrographolide, didehydro andrographolide/andrographlide D, 14deoxyandrographolide, non-bitter compound is neo andrographolide, homoandrographolide, andrographosterin, andrograpanin, αsitosterol, stigmasterol. Apigenin-7, 4-dio-methyl ether, 5-hydroxy 7,8,2, 3-tetramethoxy flavones, monohydroxy trimethyl flavones, andrographin, dihydroxy di-methoxy flavoue, panicolin, andrographoneo, andrographoside, andropani-culoside (Akbar, 2011, Singha *et al*. 2007, Choudhury *et al*. 1983) [2, 52, 13] andrograpanin, Isoandrographolide and skollcaflavone**.** Six entlabdane diterpenoids i.e. 3-o-beta-Dglucopyranosyl-14, 19-dideoxyandrographolide, 14-deox, 17-hydroxyandrographolide, 19-o-[beta-D-apiofuranosy 1-2betaD-glucopyranoyl]-3, 14-dideoxyandiographolide, 3-obeta-Dglucopyranosyl-andro-grapholide, 12S-hydroxy andrographolide and andrographatoside. These compounds showed inhibitor activity against several fungal and bacterial strains. Dua *et al*. reported four xanthones 1,8-dihydroxy3,7-dimethoxy xanthone, 4,8-di-hydroxy-2, 7-dimethoxyxanthones, 1,2-dihydroxy-6, 8-dimethoxyxanthone and 3,7,8-trimethoxy-1-hydroxyxanthone from the roots (Dua *et al*.2004) [21].

Pharmacology

The plant extracts exhibit anti-typhoid activity against *Salmonella typhi* and anti-fungal activity against *Helminthosoprium sativum*. The ether and saline extracts showed antibacterial activity against *Micrococcus pyogenes* var. *aureus*, and *Escherichia coli*. The plant is also reported to possess antihepatotoxic, antimalarial, antithrombogenic, anti inflammatory, anti-snake venom, antipyretic and immuno-stimulant properties. *Andrographis* sp. stopped the spread of the Indian flu epidemic in 1919 (Sharma *et al*.1992) [48]. *A. paniculata* is a promising herb for the treatment of many diseases, including HIV and AIDS. Andrographolide esters have been found as inhibitors of the HIV virus. The esters were non-toxic to H9 cells at 1.6 - 3.1 µg/mL concentrations. They also inhibited HIV-1 and HIV-2 virus. *A. paniculata* is a potent stimulator of immune and antigen-specific responses. Antibodies are made to counteract an invading microorganism and produce a non-specific immune response, whereby the body's macrophage cells scavenge and destroy intruders. These mechanisms make *Andrographis* sp. effective against a variety of infectious and cancer-causing agents. Dried extract of *A. paniculata* induces relaxation of the uterus by blocking voltage operated calcium channels and inhibits Ca (+2) influx (Hancke *et al*.1995) [25].

The development of bacterial resistance to currently available antibiotics has made it necessary to search for new antibacterial agents. New sources, especially natural products from plants, are being investigated because medicinal plants have been widely used for treatment of many types of acute and chronic diseases and many plants with antimicrobial activity have been reported (Dharmadasa *et al*. 2013) [19]. Within the recent years, infections have increased to a great extent and antibiotics resistance effects become an ever-increasing therapeutic problem (Cowan, 1999) [17]. Natural products of higher plants may possess a new source of antimicrobial agents with possibly novel mechanisms of action (Mahesh *et al* 2008, Ahmahad *et al*.2007) [34, 1]. They are effective in the treatment of infectious diseases while simultaneously mitigating many of the side effects that are often associated with synthetic antimicrobials (Barbour *et al*.2004) [6]. The plant *Andrographis paniculata*, is an antibacterial agent capable of counteracting the ill effects of

pathogenic microbes (Tomoko *et al*.2002, Mishra *et al*.2013, Premanath *et al*.2011, Deepak *et al*. 2014) [57, 36, 18]. The antimicrobial activity of aqueous leaf extract of *A. Paniculata* was found to have antibacterial activity against *Bacillus subtilis* and *Streptococcus aureus* (Shirisha *et al*. 2013) [50]. A similar conclusion was reached by (Manjusha *et al*.2011) [35] who found that petroleum ether, acetone, chloroform and methanol extracts of *A. paniculata* leaves and stems, exhibit significant antimicrobial potential against *Enterococcus faecalis*, *Streptococcus pyogenes*, *Klebsiella pneumonia* and *Proteus vulgaris*.

Antioxidant effects: Verma and Vinayak 2008 [58] related the antioxidant effects of the aqueous extract on liver defense systems in lymphoma bearing mice. The aqueous extract and hydro alcoholic extract of the medicinal plant A. *paniculata* showed the increase in activities such as catalase, superoxide dismutase and glutathione-S transferase enzymes and reduced lactate dehydrogenase activity. The results performed with that of aqueous extract of *A. paniculata* exhibited a greater antioxidant activity than the ethanol extract in all model systems tested. The function of Hydroalcoholic extract of *A. paniculata* possesses oxidative alterations in myocardium and confers substantial cardio protective activity by facilitating in retaining the cardiac function in a normal manner Chang *et al*. 1986 [10].

Anti-inflammatory activity

It also inhibits the production of inflammatory mediators and alleviates acute hazards at its optimal dosages. Shen *et al*. 2002 [49] observed that the andrographolide, an active component of *A. paniculata*, inhibits inflammatory responses by rat Neutrophils. It was also found to inhibit the tumorspecific angiogenesis by regulating the production of various pro and antiangiogenic factors by *in vivo* and in vitro studies. In a study by Wang *et al*.2007 [60]. A. *paniculata* was found to alleviate atherosclerotic artery stenosis induced by de endothelialization and high cholesterol diet as well as lower restenosis rate after experimental angioplasty. Further in a research by Coon *et al*. 2004 [16]. it was also found to be safe and efficacious for the relief of symptoms of uncomplicated upper respiratory tract infection.

Safety and Contraindications *Andrographis paniculata* has been perceived as safe in Traditional Chinese medicine. Although trial and error in humans may not be considered scientific, it is a way of determining whether a substance is effective or harmful. When scientists began to investigate the safety of *A. paniculata*, formal toxicological studies in animal models and human clinical trials confirmed that andrographolide and other compounds have very low toxicity. Burgos *et al*. found no subchronic testicular toxicity in male rats treated with the standardized dried extract of *A. paniculata* as evaluated by reproductive organ weight, testicular histology, ultra structural analysis of leydig cells and testosterone levels after a period of 60 days treatment Huang 1994 [27]. In mice that received oral extracts of *A. paniculata* (10kg body weight) once a day for seven days, could survive and none of the mice died. Heart, kidney, liver and spleen were found to be normal in these animals. When 500mg/kg of *A. paniculata* were given daily for ten days to mice, there was no effect on growth, appetite and stool production. The animals were energetic and results of complete blood counts were normal. As with all herbs, some people will have an allergic reaction to *A. paniculata*. The other side effect as discussed above is antifertility. Overall, evidence to date indicates that andrographolides are naturally occurring compounds with low toxicity when used appropriately

Antihyperglycemic Effect

Inhibitions of α-glycosidase and α-amylase activity and stimulation of insulin sensitivity are considered as effective strategies to lower the level of postprandial blood glucose. These enzymes involved in digestion and absorption of carbohydrates resulting in postprandial increase of blood glucose (Kajaria *et al*. 2013) [30]. Insulin resistance is mainly expressed by hyperinsulinemia and high blood glucose level and is associated with some metabolic hormonal abnormalities, such as dyslipidemia, abnormal uric acid metabolism, increased ovarian testosterone secretion, endothelial dysfunction, elevated procoagulant factors, and elevated inflammatory markers (Reaven, 2004) [43]. AP extracts and andrographolide effectively showed antihyperglycemic effect by (a) lowering blood glucose level through inhibition of α-glycosidase and α-amylase (Subramanian *et al*. 2008, Xu *et al*.2007, Chao and Lin 2010) [55, 56, 62, 11, 12]; (b) increasing insulin sensitivity and thus stimulating glucose uptake and oxidation by peripheral tissues (Subramanian *et al*.2008) [55, 56](c) controlling abnormal lipid metabolism; (d) scavenging free radicals from circulation which disrupt the plasma membrane integrity resulting in decreased number of efficient plasma membrane receptors or transporter proteins necessary to uptake glucose from the blood stream (Augustine *et al*. 2014) [5]. Blood glucose lowering effect of AP was observed in both insulin-lacking diabetic rats and normal rats in several studies (Yu *et al*.2008, Chao and Lin 2010, Gupta *et al*. 2008, Zhang *et al*.2009) [63, 11, 12, 24, 64].

Anticancer activity

Cancer is a dreadful disease caused by abnormal and uncontrolled cell division. About 6 million new incidences of cancer are reported yearly worldwide. Nature has given man a variety of useful sources of remedies to cure a number of diseases. Natural products have played a significant role in drug discovery and development, especially agents active against cancer and infectious diseases (Choudhury *et al*.1999). More than 70 per cent of all cancer deaths occurred in low-and middle-income countries. The WHO noted that tobacco use, alcohol use, low fruit and vegetable intake, and chronic infections from hepatitis B virus (HBV), hepatitis C virus (HCV) and some types of human papillomavirus (HPV) are leading risk factors for cancer in low-and middle-income countries. Deaths from cancer worldwide are projected to continue rising with an estimated 12 million deaths by 2030 (Butler, 2008) [8]

In a study, conducted by Lin *et al*. *Andrographis* had been shown to inhibit non-small cell lung cancer (NSCLC) A549 cell migration and invasion via down-regulation of phosphatidylinositol 3-kinase (PI3K)/Akt signalling pathway. Here they demonstrated that Andrographolide inhibited the expression of hypoxia-inducible factor- 1α (HIF-1α) in A549 cells. HIF-1α plays an important role in tumor growth, angiogenesis and lymph node metastasis of NSCLC. The Andrographolide induced decrease of cellular protein level of HIF- 1α was correlated with a rapid ubiquitin-dependent degradation of HIF-1α, and was accompanied by increased expressions of hydroxyl- HIF-1α and prolyl hydroxylase (PHD2), and a later decrease of vascular endothelial growth

factor (VEGF) upon the treatment of Andrographolide. The VEGF expression appeared to be a consequence of HIF-1α inactivation, because its DNA binding activity was suppressed by Andrographolide. Molecular data showed that all these effects might be mediated via TGFβ1/ PHD2/HIF-1α pathway, as demonstrated by the transfection of TGFβ1 over expression vector and PHD2 siRNA, and the usage of a pharmacological MG132 inhibitor. They also elucidated the involvement of Andrographolide in HIF-1α transduced VEGF expression in A549 cells and other NSCLC cell lines. These results highlighted the potential effects of Andrographolide,
This may be developed as a chemotherapeutic or an anti-angiogenesis agent for NSCLC in the future (Chun *et al*.2010**)**

Antifertility activity

Dry leaf powder of *Andrographis paniculata*, when fed orally to male albino rats, at a dose level of 20 mg powder per day for 60 days, resulted in cessation 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 gland. There was reduction in the weight and fluid content of the accessory glands (Akbarsha *et al*., 1990) [3]. No toxicity of andrographolide (50 mg/kg) treatment for up to 8 weeks on number and motility of sperm could be observed (Sattayasa *et al*., 2010) [47].

Hepatoprotective Effect

A.paniculata is widely used traditionally as a hepatoprotective agent and a stimulating agent for multiple enzymes of the liver. It is also used as an ingredient in the polyherbal preparations for the treatment of hepatic disorders in Ayurvedic and Unani medicine (Akbar, 2011) [2]. Along with different extracts of AP, andrographolide, neoandrographolide, 14-dexoyandrographolide, and 14-deoxy-11, 12-didehydroandrographolide compounds are also reported to have hepatoprotective effect (Handa and Sharma 1990, Kapil *et al*.1993, Roy *et al*.2010, Akowuah *et al*.2009) [49, 26, 31, 44, 4]. In a comparative study, the leaf extract and andrographolide was 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 hepatoprotective role is not solely due to the presence of andrographolide. Similar effect of crude alcohol extracts of the AP leaves against CCl4-induced liver damage was also reported by Rana and Avadhoot 1991. Handa and Sharma 1990 [26, 49] reported that andrographolide, methanol extract of whole plant, and andrographolide-free methanol extract improved liver histology in rats by 48.6%, 32%, and 15%, respectively, after CCl4-induced liver injury. Verma *et al*. 2013 [59] reported the effect of ethanol extract of AP on restoration of different enzyme after CCl4-induced liver injury. Further research using specific bioactive compounds is demanding for the better understanding of the hepatoprotective role played.

Cardiovascular activity: *Andrographis* increase the nitric oxide, cyclic guanosine monophosphate, and activity of superoxide dimutase with declines of lipid peroxide and endothelin, showed in an atherosclerotic rabbit model. These observations suggested the potential of *A. paniculata* as an antioxidant to preserve endothelial function, resulting in maintenance of the balance of nitric oxide/endothelin. In another study, *A. paniculata* verified an increase of blood clotting time, thus pre- and post-treatment with the extract of *Andrographis paniculata* before angioplasty and after surgery significantly prevented constriction of blood vessels, resulting in falling risk of subsequent closing of blood vessels (restenosis) after angioplasty procedures Wang *et al*. 1997 [61]. The arterial narrowing caused by injury to the inner lining of the blood vessels and by high cholesterol in the diet was also found to be reduced by the plant *A. paniculata*. On the relaxation of the smooth muscle wall of the blood vessels, *Andrographis* additionally showed neither antihypertensive effects by consequently resulting in lowering of blood pressure in nor adrenaline-treated rats Huang 1987 [28]. These observations showed at the potential of *A. paniculata* as a great remedy for cardiovascular therapy.

Immunological potential: *A. paniculata* could combine with modern medicines against acquired immunodeficiency syndromes (AIDS). Andrographolide, which is the important constituent of *A. paniculata*, can interrupt or modified the cellular signal transduction pathway of the virus, consequently interfering the key enzymes and viral reproduction. Stephen and Comac 2000 [53]. *Andrographis paniculata* was proposed as a potent stimulator of immune system by two approaches. First was an antigen specific response; in which antibodies were made to counteract invading microbes and the second was a nonspecific immune response; macrophage cells scavenged and destroyed invaders. Since it activated both responses, it may be effective against a variety of infectious and oncogenic agents. (Bharati *et al*.2011) [7].

Conclusion

The demand of this plant is greatly increased in the past few years for its overwhelming therapeutic potentials. Available data also clearly expresses a broad spectrum of pharmacological properties of this plant. Due to possessing extensive pharmacological activities, it can be safely regarded as one of the modern catholicons. However, the investigated pharmacological activities of AP need validation through the clinical study. Though several clinical studies were successfully completed without adverse effects or fatalities, most of them only investigated upper respiratory tract infections for a variety of conditions. Verification of the efficacy of other biological activities of AP including antidiabetic, anticancer, anti-inflammatory, and hepatoprotective activities, on human study subjects would bring a lot of benefits for the largest population of the globe. It can be clearly seen the useful as highly applicability and therapeutic effects for a variety of disorders in the near future to cure human diseases as well as some animal diseases. To fulfil this dream, the researchers might focus on multiplication of this plant to meet commercial demand besides the pharmacology study. Tissue culture techniques might be a good alternative to make AP available for researches (i.e., pharmacological study and phytochemical study to find new bioactive compounds) as well as conservation of this plant.

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