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Full Length Review Article

PHARMACOLOGICAL PROPERTIES OF ANDROGRAPHIS PANICULATA

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ABSTRACT

Andrographis paniculata Nees, a well-known plant of Indian and Chinese traditional system of medicines, commonly known as Kalmegh has drawn attention of researchers in recent times. Andrographolide, the principal bioactive phytoconstituent of the plant has shown credible anticancer, anti-inflammatory, angiogenic, antivenom, antidiabetic, antimalarial potentially in various investigations around the globe. This review contains brief discussion about active constituent and pharmacological activity of plant *Andrographis paniculata*.

INTRODUCTION

Andrographis paniculata is well known plant in bangal by the name '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. Andrographis was advertised in England as a substitute of quinine. This is widely cultivated in Southern Asia, is a 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 (Zhang, 2004). 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 (Dang, 1978). It is commonly used to prevention and treatment of the common cold in Scandinavian countries (Cacres, 1997). 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 (Pholphana *et al*., 2004).

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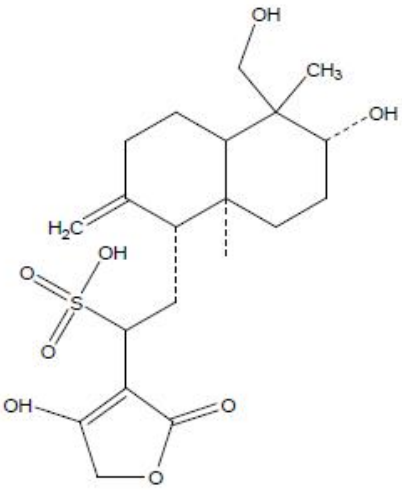
Recent research has revealed that *Andrographis paniculata* has a surprisingly broad category of pharmacological activity and some of them are enormously beneficial, such as Anti-inflammatory, (Chiou *et al*., 2000; Shen *et al*., 2002) Antidiarrhoel, (Gupta *et al*., 1990) Antiviral, (Misra *et al*., 1992) Antimalarial, (Rehman *et al*., 1999) Hepatoprotective, (Handa and Sharma, 1990) Cardiovascular, (Zhang and Tan, 1997) Anticancer, (Matsuda *et al*., 1994) and Immunostimulatory activities (Calabrese *et al*., 2000). On the other hand, male reproductive toxicity (Akbarsha and Murugaian, 2000) and cytotoxicity (Nanduri *et al*., 2004) of the plant andrographis has been reported.

Morphology of plant

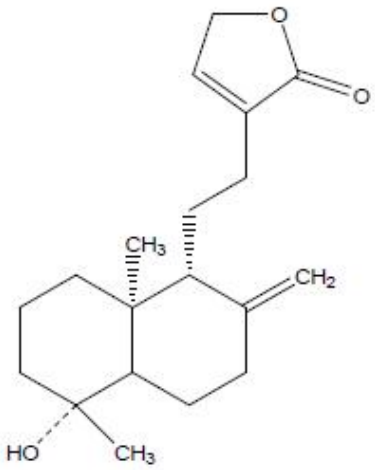
Andrographis paniculata is an annual profusely branched, erect herb extremely bitter in taste. It grows to a height of 30-110 cm in moist shady places with glabrous leaves and white flowers with rose purple spots on the petal(Figure 1).The stem dark green, 0.4-1.0 m in height, 2-6 mm in diameter, quadrangular with longitudinal furrows and wings on the angles of the younger parts, slightly enlarged at the nodes; leaves glabrous, up to 8.0 cm long and 2.6 cm broad, lanceolate, pinnate; flowers small and solitary, corolla whitish or light pink in color with hairs, in lax spreading axillary and terminal racemes or icles; capsules linear-oblong, acute at both ends, 1.9- 0.3 cm; seeds numerous, subquadrate, yellowish

brown. *Andrographis paniculata* is an annual herb found in Sri Lanka, Pakistan, Java, Malyasia, Indonesia and throughout India, specifically in Maharashtra, Karnataka, Uttar Pradesh, Tamilnadu, Andhra Pradesh and Madhya Pradesh. It is cultivated to some extent in Assam and West Bangal (Kokate *et al*., 2006).

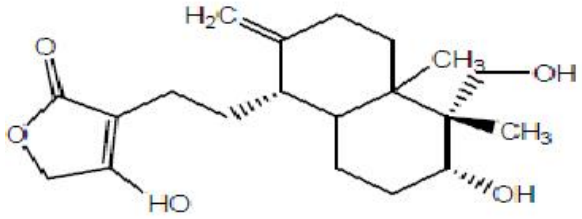
Fig. 1. Showing morphology of Andrographis paniculata



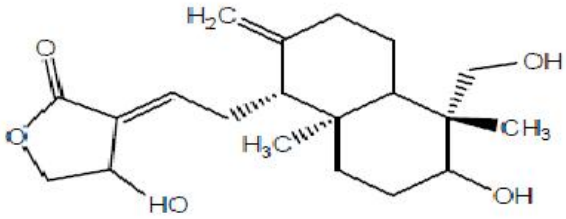
14-deoxy-12(R)-sulfo-andrographolide



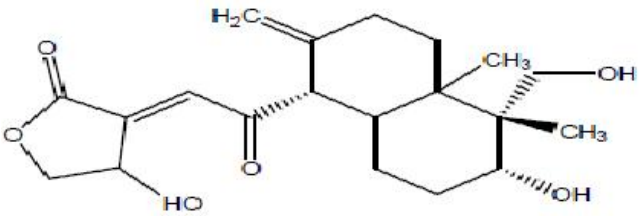
Andrograpanin



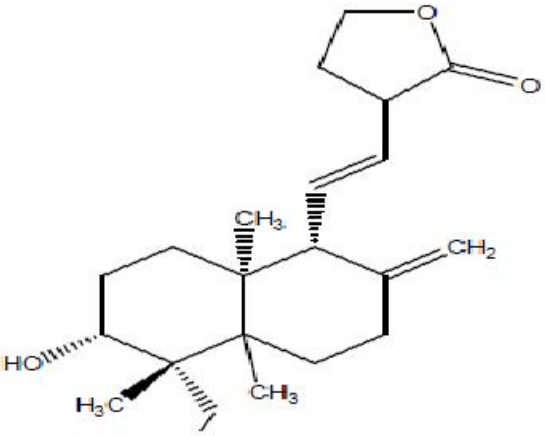
14-Deoxyandrographolide



Andrographolide



14-Deoxy-11-oxoandrographolide



14-Deoxy-11, 12-didehydroandrographolide

Fig.2. Chemical structures of some major compounds present in *Andrographis paniculata*

Chemistry

Therapeutically active constituent of kalmegh found in aerial parts. The primary active constituent of Andrographis paniculata is the Andrographolide (Chen and Liang, 1982). It is colorless bitter in taste and crystalline and known as diterpene

lactone. Investigation of *Andrographis paniculata* showed that it is a rich source of 14-deoxy-11-oxoandrographolide ($C_{20}H_{28}O_5$), 14 deoxy-11, 12- didehy droandro grapholide/ andrgraphlide D ($C_{20}H_{30}O_4$), 14 deoxyandrographolide ($C_{20}H_{30}O_4$) and other non-bitter compounds neoandrographolide ($C_{26}H_{40}O_8$); homoandrographolide ($C_{22}H_{32}O_9$); andrographosterol ($C_{23}H_{38}O$); andrographone ($C_{32}H_{64}O$); andrographane ($C_{40}H_{82}O$); andrographosterin; andrograpanin; stigmesterol; α-sitosterol; andrographin ($C_{18}H_{16}O_6$); and dihydroxy-di-methoxyflavone. Andrographolide [$C_{20}H_{30}O_5$]; (3-[2-{decahydro-6-hydroxy-5-(hydroxymethyl)-5,8α-dimethyl-2-methylene-1- napthalenyl} ethylidene]dihydro-4-hydroxy 2(3H)-furanone] is a colorless crystalline bicyclic diterpenoid lactone and present in all parts of the plant, Maximally in the leaves. On the orally consumption of andrographolide, appears to accumulate in organs throughout the viscera. Andrographolide are mainly identified as sulfonicacid adducts and sulfate compounds, as well as glucuronide conjugations. Some metabolites of andrographolide like sulfate ester compounds, sulfonates, and andrographolide analogoues were isolated from rat urine and feces. While those metabolites isolated from the human urine were like as sulfates cysteine S-conjugate, and glucuronide conjugates. One of the metabolites, 14- deoxy-12-sulfo-andrographolide was reported to be matching to the anti-inflammatory drug.

Pharmacological Potential of Plant *Andrographis paniculata*

Hepatoprotective activity

Andrographis paniculata (Kalmegh) is used extensively in the Indian traditional system of medicine as a hepatoprotective and hepatostimulative agent. The aqueous extract of the leaves of this plant has traditionally been used for treatment of various liver disorders and jaundice. Approximate 26 different remedies including *Andrographis paniculata,* used to treat liver disorders in traditional ayurvedic medicine (Handa and Sharma, 1990). Andrographolide *i.e.* main constituent of *Andrographis paniculata*, were found to be effective in preventing carbon tetrachloride induced liver damage (Rats and mice). Androgrpholide also show noteworthy hepatoprotective effect against different types of liver damage which induced by paracetamole or galactsamine, (Handa and Sharma, 1990) and had a higher capacity than a classical antioxidant silymarin in preventing a decrease of bile production induced by paracetamole (Handa and Sharma, 1990). It also played a great hepatoprotective role by reducing a lipid peroxidation product malondialdehyde (MDA), in which the lowering of MDA formation conveyed the free radical scavenging property of diterpene lactones of andrographolide, as well as by maintaining high level of glutathione, glutamic pyruvate transminase, and alkaline phosphatase in carbontetrachloride or tert-butylhydroperoxide treated mice (Kapil *et al*., 1993).Antihepatotoxic action of andrographolide was reported against *Plasmodium berghei* K173-induced hepatic damage of mastomys natalensis (Chander *et al*., 1995). Andrographolide was suggested to play an effective role as potent stimulator of gall bladder function by producing a noteworthy increase in bile flow, bile salt and bile acid in conscious rats and anesthetized guinea pigs. There was distinct improvement in the majority of infective hepatitis patient after continuous treatment with *Andrographis paniculata, i.e.*, improvement of appetite and liver function tests, regular recovery from jaundice, and subsidence of fever (Shukla *et al*., 1992).

Immunological potential

Some recent research had indicated that extract of *Andrographis paniculata*, may have the potential for interfering with the viability of the human immune-deficiency virus (HIV) and advised that *Andrographis paniculata*, could combine with modern medicines against acquired immunedeficiency syndromes (AIDS). Andrographolide, which is the important constituent of *Andrographis paniculata*,, can interrupted or modified the cellular signal transduction pathway of the virus, consequently interfering the key enzymes and viral reproduction (Stephen and Comac, 2000). *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 *Andrographis paniculata,* activated both responses, it may be effective against avariety of infectious and oncogenic agents.

Anti-cancer Potential of Andrographolide

Various anti-cancer agents inhibiting the proliferation of cancer cells by inducing apoptosis, necrosis, cell-cycle arrest or cell differentiation; others might involve immunomodulatory activity, by triggering body's own immune system against these cells. The compounds that inhibit multiple procancer events are of greater interest as they are more likely to inhibit a wider range of cancers under great variety of circumstances (Boik, 2001). Andrographolide presents a strong candidature as a therapeutic anticancer Pharmacophore as it exhibits a dual property, acting both directly and indirectly on the cancer cells (Vojdani *et al*., 2006).

Cytotoxicity against Cancer Cells

Methanolic extract of *Andrographis paniculata*, had shown noteworthy toxicity against human epidermoid leukemia and lymphocytic leukemia cell lines (Siripong *et al*., 1992). Potent cytotoxicity in a dose dependent manner towards various kinds of cancer cell lines including drug resistant cancer cells has also been reported in another excellent work (Rajagopal *et al*., 2003). The cytotoxic property has been attributed to the ability of andrographolide to inhibit proliferation and induce apoptosis in cancer cells.

Induction of Cell-cycle Arrest

At G0/G1 stage, various studies have demonstrated that andrographolide effectively induces cell-cycle arrest in cancer cells (Geethangili *et al*., 2008). A study with human acute myeloid leukemic HL-60 cells, confirmed a 27% increase in G0/G1 phase cells and significant decrease in cells at S and G2/M phase after andrographolide treatment (12 mg/ml) for 36 h. (Cheung *et al*., 2005). Andrographis inhibits cell cycle progression by modulating the expression of cell cycle related proteins. The induction of cell-cycle arrest is mainly due to the induction of cell cycle inhibitory proteins p16, p21, p27 associated with decreased expression of cyclin A, cyclin D,

CDK4 and CDK2, required for G1 to S transition (Rajagopal *et al*., 2003; Shi *et al*., 2008). Here the increased levels of p21 after andrographolide treatment (3.75-fold) are of particular interest as decreased p21 expression has been associated with aggressive phenotype in many cancers.

Anti-inflammatory and Anti-angiogenic Activity

Both Andrographis plant extract containing andrographolide are known to have an Anti-inflammatory potential (Chiou *et al*., 2000; Chiou *et al*., 1998). Mainly andrographolide treatment inhibits nuclear factor kappa B (NF-kB) binding to DNA and therefore reducing the expression of pro-inflammatory proteins such as cycloxygenase 2 (Cox-2) and nitric-oxide synthase (NOS) (Hidalgo *et al*., 2005). An important landmark in deciphering the mechanism of action of andrographolide was the finding that andrographolide reduces cysteine 62 of p50 (a major subunit of NF-kB transcription factors), therefore blocking their binding to the promoters of their target genes (Wang *et al*., 2007).Thus andrographolide as an inhibitor of NF-kB, might also be used to sensitize cancer cells to overcome such kind of resistance.

Andrographolide also play great role in the inhibition of Erk ½ and Akt signaling, thus restraining the chemo-tactic migration of macrophages on inflammation site. Inhibition of Erk signaling also leads to inhibition of v-Src oncoprotein mediated transformation, which is strongly associated with cancer initiation and progression (Liang *et al*., 2008). Cancer cells are known to induce angiogenesis for continuous supply of nutrients to the proliferating cells. As angiogenesis is triggered in response to chronic inflammation, there is a direct relation between inflammation, carcinogenesis and angiogenesis. Therefore, due to its excellent anti-inflammatory activity, andrographolide has been evaluated for its anti-angiogenic potential as well as an anti-angiogenic prospects, andrographolide could successfully inhibit the tumor specific capillary sprouting without damaging the pre-existing vasculature. *in vitro* as well as *in vivo* Andrographolide also down regulated the production of various angiogenic factors like vascular endothelial growth factor (VEGF), Nitric Oxide (NO) and pro-inflammatory cytokines and grand the levels of anti-angiogenic factors like IL-2 and tissue inhibitor of (TIMP-1) metalloproteinase (Zhao *et al*., 2008).

Anti-Hyperglycemic and Renal Protective Activities

In acute study, the chloroform extract of *Andrographis paniculata*, roots produced a dose-dependent hypoglycemia in alloxan induced diabetic rats. It produced significant reduction in blood glucose with doses of 50, 100 and 150 mg kg^{-1} body weight respectively compared to control group. At the dose of 150 mg kg^{-1} the hypoglycemic effect was observed up to 24 h. while glibenclamide produced maximum reduction of 50.44% (4 h, $p<0.01$) compared to control group. Chronic administration of *Andrographis paniculata*, to alloxan induced diabetic rats for four weeks produced significant blood glucose reduction was observed. Significant reduction was observed from the first week by both extract and glibenclamide at the doses of 150 mg/kg and 0.040 mg/kg. At the end of 4th week extract produced significant blood glucose reduction of 59.15% ($p<0.001$). On the other hand, glibenclamide produced significant blood glucose reduction of 62.02% ($p<0.001$). The activity of the extract (150 mg kg^{-1}) is not significantly different ($p<0.05$) from the standard drug glibenclamide (0.040 mg kg^{-1}). At the end of 4 weeks, major increase in urinary secretion of proteins, albumin and urea is observed in alloxan-induced diabetic rats. While no significant increase is observed in *Andrographis paniculata*, extract (150 mg kg^{-1}) and glibenclamide (0.040 mg kg^{-1}) treated group of rats (Rao and Anti, 2006).

Anti-malarial activity

Malaria is still prevalent disease in many tropical and subtropical countries. *Andrographis paniculata*, was found to considerably inhibit the multiplication of *Plasmodium berghei*, (Misra *et al*., 1992) one of the parasites which transmit the malaria. The protective action of andrographis is proposed to be due to reactivation of the key antioxidant enzyme superoxide dismutase (Chander *et al*., 1995). *Andrographis paniculata*, extracts effectively killed filarial that obstruct lymph channels consequently leading to elephantiasis, in dog. Recent research also reported Antmalarial effect of *Andrographis paniculata*, against *Plasmodium falciparum* (Rehman *et al*., 1999).

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 *Andrographis paniculata*, as an antioxidant to preserve endothelial function, resulting in maintenance of the balance of nitric oxide/endothelin. In another study, *Andrographis 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). The arterial narrowing caused by injury to the inner lining of the blood vesselsand by high cholesterol in the diet was also found to be reduced by the plant *Andrographis paniculata*. On the relaxation of the smooth muscle wall of the blood vessels, Andrographis additionally showed antihypertensive effects by consequently resulting in lowering of blood pressure in nor adrenaline-treated rats (Huang, 1987). These observations showed at the potential of *Andrographis paniculata*, as a great remedy for cardiovascular therapy.

Anti-fertility and pregnancy terminating effect

Andrographis paniculata, found to obsessed anti-fertility and pregnancy-terminating effects (Kamal *et al*., 2003) and stopped spermatogenesis in male rats. No one female mouse that daily consumed *Andrographis paniculata*, mixed food became pregnant when mated with the male of potential fertility who did not receive the treatment. The observations suggested an antispermatogenic or antiandrogenic abilities as well as ovulation preventive effect of the plant. Hence using of the herb during pregnancy should be avoided. The study pointed to a male reproductive toxic effect of a therapeutic use of andrographolide and confirmed the possible prospective use of andrographolide as a male contraceptive (Akbarsha and

Murugaian, 2000). Changes in the biochemical parameters in rats, such as significant decreases in protein content, but marked increases in cholesterol, acid phosphatase, and alkaline phosphatase levels with appearance of fructose in the reproductive system, recommended Anti-fertility effects of the andrographolide (Janarthanan and Antifertility, 1990).

In respiratory system

Andrographis paniculata, is a good remedy as treatment for common respiratory infections such as colds and flu. According to *in-vivo* research, *Andrographis paniculata*, stimulates both antigen-specific and nonspecific immune responses. Grippingly, the effects are not solely due to the andrographolide component, as the immunostimulant activity of the whole extract is greater than the isolated andrographolide constituent alone. One of the first clinical studies to be published compared the effects of two different doses of andrographis (3 or 6 g day^{-1}) to paracetamol (3.9 g day^{-1}) in the treatment of pharyngotonsillitis (Thamlikitkul, 1991). The randomised, doubleblind study involved 152 adults and found that at day 3, high-dose andrographis relieved fever and symptoms of sore throat to the same extent as treatment with paracetamol. Further, both these treatments were significantly superior to low-dose. *Andrographis paniculata*, has been tested as both a standalone treatment and in herbal combination known as Kan Jang (Swedish Herbal Institute, Gothenberg). This is a standardized prepration of *Andrographis paniculata*, extract 85 mg, containing 5.25 mg andrographolide and deoxyandrographolide per tablet and Siberian ginseng *(Eleutherococcus senticosus*) extract 9.7 mg, containing total eleutheroside B and eleutheroside E 2% (Melchior, 2000).

Antivenom Activity

Orally administration of Plant extracts of *Andrographis paniculata*, (7.2 mg kg^{-1} body weight) and particularly purefied fractions (2.4 mg kg^{-1} body weight) to mice experimentally envenomed with rattle snake venom s. c. injection (2.5-15 mg kg^{-1} body weight) showed potent neutralizing effect against the venom (rattle snake). The isolated fractions effectively inhibited the toxic effect of rattle snake venoms in vitro than *in vivo* (Samy *et al*., 2008).

Conclusions

It can be easily concluded from whole review that *Andrographis paniculata*, is an important medicinal plant. This plant contains many active chemical constituent that show definite pharmacological effect. It can be easily predicted from the findings of the articles that *Andrographis paniculata*, have antiinflammatory, antidiabetic, anticancerous, antimalarial, antiangiogenic, anti venoum and antimicrobial activity. So this plant has important medicinal value in traditional therapeutics.

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